Safety of etravirine in HIV-1/hepatitis B and/or C virus co-infected patients: pooled 96 week results from the Phase III DUET trials

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Objectives: Human immunodeficiency virus (HIV)-infected patients are frequently co-infected with hepatitis B and/or C virus (HBV/HCV). The safety of etravirine was investigated over 96 weeks in patients co-infected with HIV type-1 (HIV-1) and HBV and/or HCV in the Phase III DUET trials. DUET-1 and DUET-2 are registered with clinicaltrials.gov (NCT00254046 and NCT00255099, respectively).

Methods: Treatment-experienced, HIV-1-infected patients with documented non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance were randomized to receive either etravirine 200 mg or placebo, both twice daily plus a background regimen of darunavir/ritonavir, investigator-selected nucleoside reverse transcriptase inhibitors and optional enfuvirtide. Hepatitis co-infection status was confirmed by hepatitis B surface antigen or HCV antibody and qualitative HCV RNA. Co-infected patients were eligible if they did not require anti-hepatitis treatment and were clinically stable, with aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations ≤5× the upper limit of normal. Adverse events (AEs) and laboratory parameters were analysed.

Results: Data were available for 566 etravirine- and 564 placebo-treated patients, of whom 72 (13%) and 68 (12%), respectively, were co-infected with HBV/HCV. Irrespective of co-infection status, the etravirine and placebo groups were comparable for the incidence of grade 3/4 AEs [co-infected: 31 (43%) versus 31 (46%) patients, respectively; non-co-infected: 200 (40%) versus 176 (35%), respectively] and serious AEs [co-infected: 25 (35%) versus 25 (37%), respectively; non-co-infected: 123 (25%) versus 119 (24%), respectively]. Consistent with the underlying hepatitis, relative to non-co-infected patients the co-infected patients, had a higher incidence of hepatic AEs [co-infected: 13 (18%) etravirine-treated versus 10 (15%) placebo-treated patients; non-co-infected: 36 (7%) versus 32 (6%), respectively] and grade 3/4 elevation of AST [co-infected: 8 (11%) versus 5 (7%), respectively; non-co-infected: 14 (3%) versus 9 (2%), respectively] and ALT [co-infected: 10 (14%) versus 6 (9%), respectively; non-co-infected: 14 (3%) versus 8 (2%), respectively]. Discontinuation due to hepatic AEs was low and comparable between the treatment groups, regardless of co-infection status (two co-infected patients in each treatment group; five etravirine-treated versus two placebo-treated non-co-infected patients).

Conclusions: Etravirine demonstrated a similar safety profile to placebo in the subgroup of patients co-infected with HIV and HBV and/or HCV in the DUET trials. The incidence and severity of AEs with etravirine was generally comparable to placebo irrespective of co-infection status.

Keywords: treatment experienced, non-nucleoside reverse transcriptase inhibitors, TMC125, HBV, HCV

Introduction

Worldwide, an estimated 4–5 million people are co-infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV), and 2–4 million people are co-infected with HIV and hepatitis B virus (HBV).1 The presence of HIV is known to alter the clinical course of HBV and HCV infection, often accelerating the progression of hepatitis-related liver disease.2 Indeed, elevated
plasma HIV RNA is thought to be responsible for the accelerated hepatic fibrosis often observed in co-infected patients, and controlling HIV viral load is important in order to slow down the progression of chronic liver disease.3

Although effective for the treatment of HIV, some currently available antiretroviral (ARV) agents are known to cause hepatic toxicity,4,5 and patients co-infected with HBV and/or HCV may be more likely to experience hepatic adverse events (AEs) and be at increased risk of liver-related morbidity and mortality. An assessment of the safety and tolerability of agents used for the treatment of HIV in hepatitis co-infected patients is therefore imperative.

The non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine is approved for use in combination with other ARV agents in treatment-experienced, HIV-1-infected patients. The durable efficacy and favourable tolerability profile of etravirine have been demonstrated in the Phase III DUET (TMC125 to Demonstrate Undetectable viral load in patients Experienced with ARV Therapy) trials.5,6 The safety of etravirine in the subset of patients co-infected with HBV and/or HCV was also investigated in the DUET trials and the results at 96 weeks are presented here.

Methods

The DUET trials were randomized, double-blind trials designed to investigate the efficacy and safety of etravirine versus placebo, both in combination with a background regimen (BR) of the protease inhibitor (PI) darunavir/ritonavir, investigator-selected nucleoside reverse transcriptase inhibitors (NRTIs) and optional enfuvirtide, in treatment-experienced, HIV-1-infected patients with documented NNRTI resistance. Patients received treatment for 48 weeks, after which time they could continue into an open-label, optional extension period to 96 weeks. Patients in both treatment groups were permitted to withdraw from the trial after 48 weeks at the investigator’s discretion. Full details of the DUET study design and methodology have been published previously.5

This was a pre-planned subgroup analysis in patients co-infected with HIV-1 and HBV and/or HCV (results of post hoc analyses are also included where relevant). Co-infected patients were eligible to participate if they were clinically stable, did not require anti-hepatitis treatment and had aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations less than five times the upper limit of normal.

Patients were excluded if they had any active, clinically significant disease or acute viral hepatitis including, but not limited to, A, B or C. HBV and/or HCV co-infection was defined as having a positive hepatitis B surface antigen and/or active HCV infection, which was determined based on the HCV antibody and RNA results. The model for end-stage liver disease (MELD) score,8 useful for estimating the survival probability of a patient with end-stage liver disease, was used to determine liver disease stage and was calculated using the last available laboratory results (serum bilirubin, creatinine and prothrombin time) prior to baseline. The MELD score is divided into five ranges: <10; 10–19; 20–29; 30–39; and 40 (with a score of ≤10 indicating the least sick patient and 40 the most sick patient).

AEs and laboratory abnormalities were routinely monitored and recorded using the Division of Acquired Immunodeficiency Syndrome grading scale. No statistical testing on this subgroup was performed as the studies were not powered for this.

All patients gave written, informed consent. The trial protocol was reviewed and approved by Independent Ethics Committees or Institutional Review Boards, and the trials were conducted in accordance with the Declaration of Helsinki and the European Union Clinical Trials Directive. DUET-1 and DUET-2 are registered with clinicaltrials.gov (NCT00254046 and NCT00255099, respectively).

Results

Hepatitis co-infection status was available for 566 and 564 patients in the etravirine and placebo groups, respectively. Of these, 72 (13%) etravirine- and 68 (12%) placebo-treated patients were co-infected with HBV and/or HCV, accounting for ~12% of the total population. Separate analyses of HBV and HCV were not meaningful due to small patient numbers. Baseline characteristics were generally comparable between the treatment groups, irrespective of hepatitis co-infection status (Table 1). However, compared with the other subgroups, a higher percentage of patients in the etravirine group co-infected with HBV and/or HCV were classed as CDC category C (48 patients (67%)) and these patients also had lower median CD4 cell count (92.5 cells/mm3), suggesting that this subgroup of patients had slightly more advanced disease. The majority of patients (≥87%) had a MELD score of ≤10 (Table 1).

Duration of study treatment and total patient-years of exposure were longer in the etravirine group than in the placebo group; median treatment duration was 96 weeks in the etravirine-treated subgroups, compared with 90 weeks in the placebo co-infected subgroup and 70 weeks in the placebo non-co-infected subgroup. The incidence of AEs, grade 3 or 4 AEs, serious AEs and discontinuations due to AEs was comparable between the treatment groups in both co-infected and non-co-infected patients (Table 2); all comparisons between etravirine and placebo in the co-infected and non-co-infected subgroups were non-significant (P > 0.05), except for rash (see below). Overall, 96%–97% of patients in each treatment group experienced AEs. Serious AEs were reported in 35% and 37% of co-infected patients in the etravirine group, versus 9% and 12% of non-co-infected patients, respectively, in 25% and 24% of non-co-infected patients, respectively.

The most common AEs in ≥10% of co-infected patients in the etravirine group were nausea [12 patients (17%)], diarrhoea [11 patients (15%)], injection-site reaction [10 patients (14%)], pyrexia [9 patients (13%)], cough [9 patients (13%)], oral candidiasis [8 patients (11%)] and anaemia [8 patients (11%)]. Hepatic AEs and increases in liver enzymes (AST and ALT) were more frequently observed in co-infected patients than in non-co-infected patients in both treatment groups; however, the incidence of hepatic AEs was generally comparable between the etravirine and placebo treatment groups (co-infected: 13 (18%) versus 10 (15%) patients, respectively; non-co-infected: 36 (7%) versus 32 (6%), respectively). Discontinuations due to hepatic AEs were infrequent and comparable between the treatment groups (two co-infected patients from each group, five etravirine-treated and two placebo-treated non-co-infected patients).

The incidence of rash, although higher in etravirine-treated patients, was similar in co-infected and non-co-infected patients in each treatment group (21% of co-infected and non-co-infected patients in the etravirine group, versus 9% and 12% of patients in the placebo group, respectively). The incidence of rash in the subgroup of non-co-infected patients was significantly higher with etravirine than placebo (P = 0.0002; Fisher’s exact test). Neither treatment group nor co-infection status
had an impact on the incidence of neuropsychiatric AEs (co-infected: 31% etravirine-treated versus 34% placebo-treated patients; non-co-infected: 34% versus 37%, respectively).

**Discussion**

Analysis of the pooled results from the DUET trials indicates that etravirine has a similar safety profile to placebo in patients co-infected with HIV-1 and HBV/HCV. In general, the incidence and severity of AEs was comparable between the etravirine and placebo groups, irrespective of co-infection status. As might be expected, and consistent with the underlying hepatitis co-infection, the incidence of hepatic AEs was higher in co-infected patients than in non-co-infected patients, regardless of treatment arm. However, the percentage of co-infected patients reporting hepatic AEs was not significantly different in the etravirine and placebo groups, suggesting that etravirine in combination with a BR does not increase hepatotoxicity versus placebo in co-infected patients.

In addition, consistent with the results reported for the overall DUET population, the incidence of rash was higher with etravirine than with placebo irrespective of co-infection status, while the incidence of neuropsychiatric AEs was similar between the treatment groups.

Several studies have explored the safety of ARVs in hepatitis co-infected patients, with a particular focus on hepatic AEs. Ammassari and colleagues investigated the role of different ARV classes (PIs, NRTIs and NNRTIs) on ALT elevation in co-infected and non-co-infected patients and found that no particular class was associated with elevated ALT. However, in a multivariate analysis, HCV co-infection and duration of HIV treatment were associated with elevated ALT levels. Conversely, Torti and colleagues reported that the risk of hepatotoxicity was higher in treatment-experienced, co-infected patients taking NNRTI therapy (efavirenz or nevirapine) compared with those taking PIs. It has also been shown that use of some first-generation NNRTIs in hepatitis co-infected patients can increase the risk of symptomatic events and asymptomatic increases in ALT/AST.

The present analysis has several limitations. The number of patients co-infected with HBV and/or HCV was relatively small, at only 12% of the total DUET patient population, which limits the conclusions that can be drawn from statistical comparisons and individual analyses of results in co-infected patients. The duration of treatment differed between the groups, with non-co-infected patients in the placebo group undergoing a median of 70 weeks’ treatment, compared with 90 weeks in co-infected placebo patients and 96 weeks in both etravirine groups. In addition, patients were excluded if they presented with severe liver disease at baseline and the safety of etravirine in this patient population has not been investigated. The use of darunavir in the BR could potentially have confounded the results as drug-induced hepatitis has been reported with darunavir/ritonavir therapy, although a causal relationship with darunavir/ritonavir has not been established.
Within these limitations, the data from this analysis suggest that etravirine in combination with a BR has a tolerability profile similar to that of placebo in patients co-infected with HIV and HBV and/or HCV. These results confirm the observations at 48 weeks and provide longer-term evidence of the safety and tolerability of etravirine in treatment-experienced, HIV-1-infected patients with HBV and/or HCV.

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Table 2. Safety results by hepatitis co-infection status at 96 weeks

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<td><strong>HBV and/or HCV co-infected patients</strong></td>
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<td>etravirine + BR (n = 72)</td>
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<td><strong>HBV and/or HCV non-co-infected patients</strong></td>
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Most common AEs, n (%)

- nausea: 12 (17) vs. 16 (24), 0.65 (0.28; 1.50)
- diarrhoea: 11 (15) vs. 15 (22), 0.64 (0.27; 1.51)
- injection-site reaction: 10 (14) vs. 12 (18), 0.75 (0.30; 1.88)
- pyrexia: 9 (13) vs. 10 (15), 0.83 (0.31; 2.18)
- cough: 9 (13) vs. 6 (9), 1.48 (0.50; 4.39)
- oral candidiasis: 8 (11) vs. 7 (10), 1.09 (0.37; 3.19)
- anaemia: 8 (11) vs. 3 (4), 2.71 (0.69; 10.67)
- Hepatic AEs, n (%)
  - grade 3 or 4 hepatic AEs: 8 (11) vs. 5 (7), 1.58 (0.49; 5.08)
  - serious hepatic AEs: 3 (4) vs. 4 (6), 1.17 (0.39; 3.52)
  - discontinuation due to hepatic AE: 2 (3) vs. 1 (2), 2.53 (0.49; 13.08)
- Grade 3 or 4 laboratory abnormalities, n (%)
  - ALT: 10 (14) vs. 6 (9), 1.67 (0.57; 4.87)
  - AST: 8 (11) vs. 5 (7), 1.58 (0.49; 5.08)
- AEs of interest, n (%)
  - rash: 15 (21) vs. 6 (9), 2.72 (0.99; 7.49)
  - neuropsychiatric AEs: 22 (31) vs. 23 (34), 0.86 (0.42; 1.75)

CI, confidence interval.
HBV and/or HCV status was not recorded in 33 etravirine- and 40 placebo-treated patients; these patients are not included in the analysis.
All comparisons between etravirine and placebo in the co-infected and non-co-infected subgroups were non-significant (P > 0.05; Fisher's exact test), except for rash in the non-co-infected subgroup (P = 0.0002; Fisher's exact test).

aAll deaths in the etravirine + BR group were considered not or doubtfully related to etravirine. One death in the placebo + BR group was considered possibly related to the BR.
bIn ≥10% of etravirine-treated co-infected patients.

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GlaxoSmithKline, Janssen-Cilag, Merck Sharp & Dohme, Panacos, Pfizer, Roche and Tibotec. N. C. has participated as an expert or investigator for Abbott, Boehringer-Ingelheim, Gilead Sciences, GlaxoSmithKline, Merck Sharp & Dohme, Pfizer, Roche and Tibotec. C. K. has no further conflict of interest. S. N. and J. W. are full-time employees of Tibotec. B. C., N. C., C. K. and S. N. do not own stock in any relevant companies; J. W. owns stock in Johnson & Johnson.

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Author contributions

B. C., N. C. and C K. are study investigators and participated in the recruitment of patients and reporting of data for the patients they enrolled. S. N. and J. W. contributed to the design, conduct and analysis of the DUET trials. All authors were involved in the interpretation of the data, reviewed and revised the manuscript for intellectual content, and approved the final version for submission. B. C. and J. W. had access to the full data and act as guarantors for the data.

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