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Cost-minimisation analysis of the use of etravirine or raltegravir in treatment-experienced HIV-1-infected patients

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Abstract

HIV treatment guidelines state that the goal of highly active antiretroviral therapy (HAART) is to achieve an undetectable viral load (<50 copies/mL) in HIV-infected patients. Two new therapies, etravirine (ETR; TMC125) and raltegravir (RAL), have recently been approved in the USA, both with similar indications for treatment-experienced HIV-1-infected patients. This analysis compared the relative cost of reaching this treatment goal for each therapy.

The proportion of patients achieving undetectable viral load (<50 copies/mL) was reported in Phase III trials that compared ETR (DUET-1 and DUET-2) or RAL (BENCHMRK-1 and BENCHMRK-2) to placebo, both in the presence of a background regimen (BR). ETR and RAL have not been compared in head-to-head trials, so an indirect comparison of efficacy and cost of treatment at Week 24 was made. In both sets of trials, patients were treatment-experienced, but the composition of the BR differed. In DUET, all patients received darunavir with low-dose ritonavir (DRV/r) as part of their BR, while in the BENCHMRK trials less than half of the patients received background DRV/r. Subgroup data from BENCHMRK provided a 'prior' estimate of the treatment effect modification due to DRV/r use. A Bayesian analysis was used, which adjusted for differences in background DRV/r use between trials. The current analysis estimated the treatment effect assuming that all patients received background DRV/r. After adjusting for differences in the trials, efficacy and US wholesale acquisition drug costs were analysed.

ETR and RAL demonstrated a similar treatment effect when adjusting for differences in the BR. Mean odds ratios (95% confidence interval) versus placebo were 2.08 (1.63–2.61) and 1.92 (1.08–3.42) for ETR and RAL, respectively. Annual drug costs were calculated to be US$7,957 for ETR and US$10,435 for RAL.

Both ETR and RAL showed similar efficacy rates in achieving undetectable viral load. As a result, a cost-minimisation approach can be taken when evaluating the addition of ETR or RAL to a HAART regimen for treatment-experienced HIV-1-infected patients.

Introduction

- US Department of Health and Human Services guidelines state the goal of HAART is to reduce viral load to undetectable levels (<50 copies/mL)[1]
- Two therapies have recently been introduced in the USA with similar indications for treatment-experienced patients: ETR and RAL
- The DUET-1 and DUET-2 trials evaluated the efficacy of the next generation NNRTI ETR versus placebo, given with a BR of NRTIs, DRV/r and optional ENF, in highly treatment-experienced patients
- The BENCHMRK-1 and BENCHMRK-2 trials evaluated the efficacy of RAL versus placebo, given with a BR of NRTIs, PIs, and optional ENF, in highly treatment-experienced patients
- A recent network meta-analysis of these trials by Hawkins et al.[2] found that when the results are adjusted for background DRV/r, the predicted effects of both RAL and ETR are similar

BR = background regimen; ENF = enfuvirtide; PI = protease inhibitor

Etravirine (INTELENCE™) US indication[3]

Indications and usage*

- INTELENCE™, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients, who have evidence of viral replication and HIV-1 strains resistant to a non-nucleoside reverse transcriptase inhibitor (NNRTI) and other antiretroviral agents
- This indication is based on Week 24 analyses from 2 randomized, double-blind, placebo-controlled trials of INTELENCE™. Both studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, N[t]RTI, PI) treatment-experienced adults
- The following points should be considered when initiating therapy with INTELENCE™:
  - treatment history and, when available, resistance testing, should guide the use of INTELENCE™
  - the use of other active antiretroviral agents with INTELENCE™ is associated with an increased likelihood of treatment response
  - in patients who have experienced virologic failure on an NNRTI-containing regimen, do not use INTELENCE™ in combination with only N[t]RTIs [*see Clinical Studies (14)*]
  - the risks and benefits of INTELENCE™ have not been established in pediatric patients or in treatment-naïve adult patients

*Text taken from INTELENCE US prescribing information, 2008

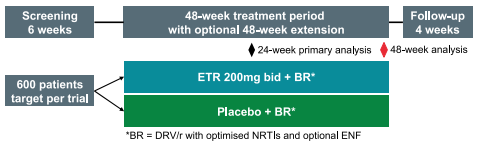
Raltegravir (ISENTRESS®) US indication[4]

Indications and usage*

- ISENTRESS in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents
- This indication is based on analyses of plasma HIV-1 RNA levels up through 24 weeks in two controlled studies of ISENTRESS. These studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, NRTI, PI) treatment-experienced adults
- The use of other active agents with ISENTRESS is associated with a greater likelihood of treatment response *[see Clinical Studies (14)]*
- The safety and efficacy of ISENTRESS have not been established in treatment-naïve adult patients or pediatric patients
- There are no study results demonstrating the effect of ISENTRESS on clinical progression of HIV-1 infection

*Text taken from ISENTRESS US prescribing information, 2008

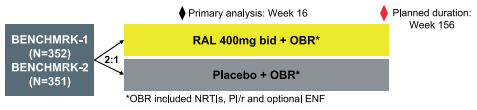
DUET study design and major inclusion criteria[5,6]



*BR = DRV/r with optimised NRTIs and optional ENF

- DUET-1 and DUET-2 differed only in geographical location; pooled analysis was prespecified
- Major inclusion criteria
  - plasma viral load >5,000 HIV-1 RNA copies/mL and stable therapy for ≥8 weeks
  - ≥1 NNRTI mutation at screening or in documented historical genotype
  - ≥3 primary PI mutations at screening
- Patients were recruited from Thailand, Australia, Europe and the Americas

BENCHMRK study design and major inclusion criteria[7]



*OBR included NRTIs, PI/r and optional ENF

- Major inclusion criteria
  - HIV-1-infected, triple-class resistant patients
  - plasma viral load >1,000 HIV-1 RNA copies/mL
  - no CD4 cell count cut-off
- Patients were recruited from Europe, Peru and Asia-Pacific (BENCHMRK-1) and North and South America (BENCHMRK-2)

Baseline characteristics

Parameter	DUET-1[5] ETR + BR	DUET-1[5] Placebo + BR	DUET-2[6] ETR + BR	DUET-2[6] Placebo + BR	BENCHMRK-1[8] RAL + OBR	BENCHMRK-1[8] Placebo + OBR	BENCHMRK-2[8] RAL + OBR	BENCHMRK-2[8] Placebo + OBR
Mean age, years	45	45	46	45	46	44	45	47
Male, %	87	86	94	92	84	87	91	90
Caucasian, %	65	65	77	76	75	81	55	65
Mean CD4 cell count, cells/mm^3	99	109	100	108	156	153	146	163
Mean $\log_{10}$ HIV RNA, copies/mL	4.8	4.9	4.8	4.8	4.6	4.5	4.7	4.7
Median duration of HIV infection, years	13.4	13.3	14.5	15.1	NS	NS	NS	NS
Hepatitis B/C co-infected, %	12	11	13	13	21	23	12	8
3-class treatment experienced*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

*NNRTI, NRTI and PI; NS = not stated

Background treatments

Proportion of patients receiving, %	DUET-1[5] ETR + BR (N=304)	DUET-1[5] Placebo + BR (N=308)	DUET-2[6] ETR + BR (N=295)	DUET-2[6] Placebo + BR (N=296)	BENCHMRK-1[8] RAL + OBR (N=232)	BENCHMRK-1[8] Placebo + OBR (N=118)	BENCHMRK-2[8] RAL + OBR (N=230)	BENCHMRK-2[8] Placebo + OBR (N=119)
RAL	0	0	0	0	100	0	100	0
ETR	100	0	100	0	0	0	0	0
DRV/r	100	100	100	100	33	30	47	54
ENF *de novo*	24	26	27	27	21	20	19	20

NRTIs were also included as part of the BR in each trial

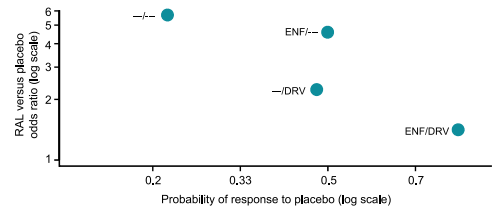
Summary of Week 24 endpoint results

	DUET-1[5] ETR + BR (N=304)	DUET-1[5] Placebo + BR (N=308)	DUET-2[6] ETR + BR (N=295)	DUET-2[6] Placebo + BR (N=296)	BENCHMRK-1[8] RAL + OBR (N=232)	BENCHMRK-1[8] Placebo + OBR (N=118)	BENCHMRK-2[8] RAL + OBR (N=230)	BENCHMRK-2[8] Placebo + OBR (N=119)
Patients with HIV RNA <50 copies/mL, n (%)	170 (56)	119 (39)	183 (62)	129 (44)	142 (61)	39 (33)	149 (65)	41 (34)

In addition to the primary comparators, a BR including NRTIs, DRV/r and optional ENF for ETR, and NRTIs, PI/r and optional ENF for RAL was also administered

- HIV RNA <50 copies/mL was the primary endpoint of the DUET trials
- HIV RNA <400 copies/mL was the primary endpoint of the BENCHMRK trials

Relationship between RAL treatment effect and background DRV/r and de-novo ENF use and placebo response



- Published subgroup analysis suggest that background use of either de-novo ENF or DRV increases the absolute probability of response to both RAL and placebo, and decreases the response to RAL relative to placebo on the odds ratio scale[2,7]

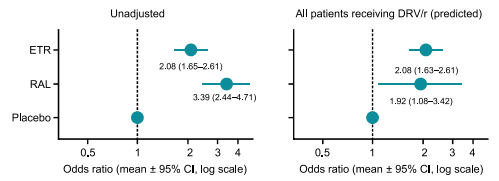
Impact of background therapy on RAL treatment effect in the BENCHMRK trials

Covariable	Modification of RAL treatment effect odds ratio (multiplier per unit increase) Mean	2.5% CI	97.5% CI
Background DRV/r use	0.386	0.155	0.794
Background de-novo ENF use	0.717	0.249	1.616

- Combined BENCHMRK data were analysed with regression analysis to provide estimates of the treatment modifying effect of background DRV/r and de-novo ENF on RAL relative to placebo
- Background DRV/r use was found to have a significant effect on the RAL treatment effect odds ratio relative to placebo[2]

Cost-minimisation analysis is possible when similar efficacy is seen between agents

- The treatment effect of ETR and RAL on the <50 copies/mL endpoint are similar when adjusting for DRV/r use in the RAL arm using a published subanalysis[2]



- Annual drug cost September 2008 (WAC, Analy$ource.com)
  - ETR: US$7,957
  - RAL: US$10,435

WAC = wholesale acquisition cost

Conclusions

- ETR and RAL were studied in similar patient populations, and have similar indications to treat HIV-1-infected adult patients in the USA
- Based on the results showing similar efficacy rates in reaching the treatment goal of <50 copies/mL, a cost-minimisation approach can be taken when evaluating the addition of ETR or RAL to a HAART regimen for treatment-experienced patients
- Applying the cost-minimisation approach, ETR costs US$2,478 less than RAL to add to a regimen for treatment-experienced HIV patients
- This analysis does not account for additional savings in hospitalisations[9] or reductions in AIDS-defining illnesses and deaths[10] that have been shown to be associated with ETR

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