TUPE0059

The incidence of rash observed with the NNRTI etravirine in the Phase III DUET trials using pooled 48-week data

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Abstract

Background

Rash is a known side effect of HIV therapy. We present a detailed analysis of rash in the ongoing, randomized, placebo-controlled, multicenter, Phase III DUET trials using pooled 48-week data.

Methods

Treatment-experienced patients with NNRTI resistance and ≥3 primary protease inhibitor (PI) mutations were randomized to receive etravirine (ETR; TMC125) 200mg or placebo, both bid, with a background regimen (BR) consisting of darunavir with low-dose ritonavir 600/100mg bid (DRV/r), investigator-selected NRTI(s) ± enfuvirtide (ENF). Safety and tolerability are being assessed throughout the trials.

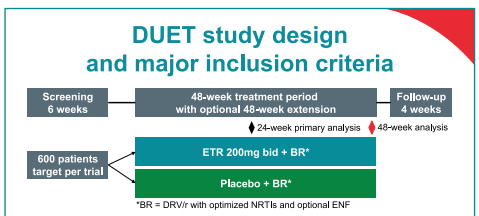
Results

One thousand, two hundred and three patients were included in the analysis (median age 45 years, 10.7% female, median baseline viral load 4.8 $\log_{10}$ copies/mL, CD4 cell count 105 cells/mm^3); 599 received ETR and 604 placebo. The incidence of rash was 19.2% (ETR) vs 10.9% (placebo) (p<0.0001). Most rashes were mild-to-moderate with ETR (1.3% grade 3, none grade 4), generally occurred early during treatment (median onset 14 days), were of limited duration (median 15 days) and infrequently led to discontinuation (2.2%). At timepoints after the first 6 weeks of treatment, the incidence of rash with ETR was low and similar to placebo. Rash was mostly maculopapular; no cases of Stevens-Johnson syndrome (SJS), erythema multiforme or toxic epidermal necrolysis were reported in the ETR group in the DUET trials. CD4 cell count or a history of NNRTI-related rash were not predictive of rash with ETR, and no relationship to pharmacokinetic (PK) exposure was evident. In the ETR group, rash occurred with a higher incidence in women than in men (30% vs 18%, respectively); there were no differences in severe rash or discontinuations due to rash between genders. There was no specific pattern of laboratory abnormalities associated with rash.

Conclusions

In the DUET trials, rashes did occur more frequently with ETR than placebo. Rashes were mostly mild-to-moderate, occurred early and infrequently led to discontinuation.

DUET study design and major inclusion criteria



Baseline characteristics and background ARVs

Parameter	ETR + BR (n=599)	Placebo + BR (n=604)
Patient demographics		
Male, %	90	89
Caucasian, %	70	70
Patient history		
Previous NNRTI use, %	92	92
EFV	70	73
NVP	57	59
Previous DRV/r use, %	4	5
NNRTI-associated rash, %	8	14
Disease characteristics		
Viral load, $\log_{10}$ copies/mL (range)	4.8 (2.7–6.8)	4.8 (2.2–6.5)
CD4 cells, cells/mm^3 (range)	99 (1–789)	109 (0–812)
CDC category C, %	58	59
Detectable mutations		
≥2 NNRTI RAMs, %	69	69
≥3 primary PI RAMs, %	38	37
BR		
Used ENF (total), %	46	47
Used ENF *de novo*, %	26	26

ARV = antiretroviral; EFV = efavirenz; NVP = nevirapine

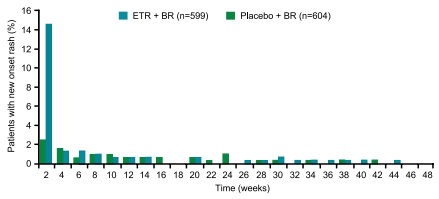
Overview of AEs (regardless of causality) after 48 weeks of treatment

Parameter	ETR + BR (n=599)	Placebo + BR (n=604)
Treatment duration, weeks	**52**	**51**
Any AE (any cause), %	**96**	**96**
Grade 3 or 4 AE	33	35
Discontinuation due to AE	7	6
Serious AE	20	23
Death (any cause)*	2	3
Most common AEs[‡,§]		
Rash (any type)	19	11
Diarrhea	18	24
Nausea	15	13
Headache	11	13
Nasopharyngitis	11	10
AEs of interest, %		
Nervous system disorders	17	20
Psychiatric disorders	17	20
Hepatic AEs	7	6

*All deaths in the ETR group were considered not or doubtfully related to ETR. One death in the pooled placebo group was considered possibly related to the BR; ‡Occurring in at least 10% of patients in the ETR group

AE = adverse event

Rash (any type) incidence over time



- Rash was most frequent during the first 2 weeks of ETR therapy
- For patients in the ETR group
  - median onset 14 days
  - median duration 15 days

Rash (any type) overview after 48 weeks of treatment

Parameter	ETR + BR (n=599)	Placebo + BR (n=604)
Any rash AE, %	**19**	**11**
Grade 1	10	8
Grade 2	9	4
Grade 3	1*	0
Grade 4	0	<1‡
Discontinuation due to rash, %	2	0
Median onset, days	14	50
Median duration, days	15	26

*Eight patients in the ETR group reported grade 3 rash; ‡The one grade 4 rash (SJS) was likely related to an allergic reaction to trimethoprim/sulfamethoxazole

- For the majority of patients rash was mild-to-moderate in severity
- Rate of discontinuation was low in the ETR group

SJS = Stevens-Johnson syndrome

Patients with grade 3 rash

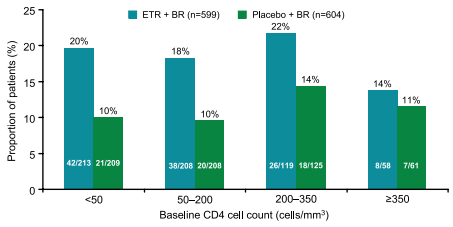
Gender	History of NNRTI-related rash/other drug allergy	Onset in trial (day)	Duration (days)	Systemic symptoms*	Hepatic abnormalities*	Action taken
Male	None/none	77	>146	Cellulitis,† sepsis,† diarrhea, renal failure†	None	None
Male	None/none	15	8	None	None	Permanent stop
Female	None/ATV, LPV/r	9	11	None	None	Permanent stop
Female	EFV/cefalexina	8	15	None	Grade 2 ALT increase	Permanent stop
Male	NVP/none	11	>3	None	None	Permanent stop
Male	None/AZT, Iodine	11	>36	None	None	Permanent stop
Male	None/none	12	13	Diarrhea, headache, nausea, night sweats, vomiting	None	Temporary stop
Male	None/none	2	13	Fatigue, myalgia, nausea	None	Permanent stop

*Systemic symptoms/hepatic abnormalities ongoing or emerging during the occurrence of rash; †Reported as a serious AE

- Grade 3 rashes were maculopapular in nature with no mucosal involvement

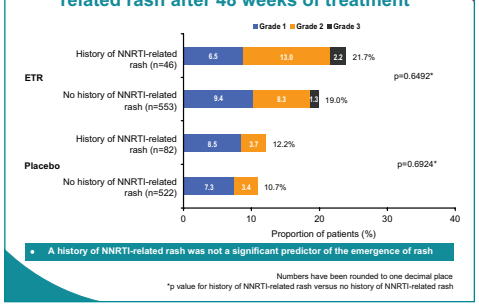
ATV = atazanavir; LPV/r = lopinavir/ritonavir; ALT = alanine aminotransferase; AZT = zidovudine

Rash (any type) incidence by baseline CD4 cell count after 48 weeks of treatment



- No relationship between incidence of rash and baseline CD4 cell count was noted for ETR

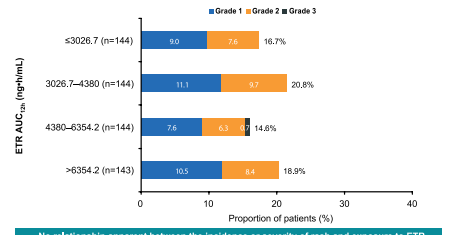
Rash (any type) incidence by history of NNRTI-related rash after 48 weeks of treatment



- A history of NNRTI-related rash was not a significant predictor of the emergence of rash

Numbers have been rounded to one decimal place
*p value for history of NNRTI-related rash versus no history of NNRTI-related rash

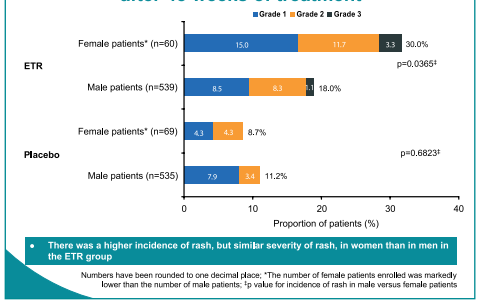
Rash (any type) incidence by ETR PK exposure* after 48 weeks of treatment



- No relationship apparent between the incidence or severity of rash and exposure to ETR

AUC_{12h} = area under the plasma concentration–time curve from time of administration to 12 hours after dosing
Numbers have been rounded to one decimal place
*Patient AUC_{12h} data were divided into subgroups: 3026.7ng•h/mL, 4380ng•h/mL (median), 6354.2ng•h/mL

Rash (any type) incidence by gender after 48 weeks of treatment



- There was a higher incidence of rash, but similar severity of rash, in women than in men in the ETR group

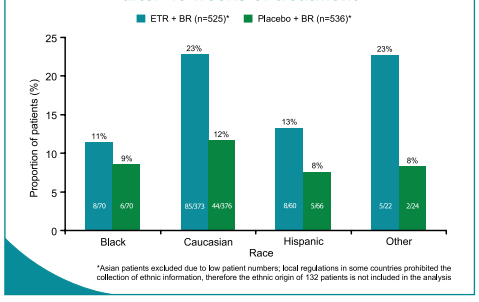
Numbers have been rounded to one decimal place; *The number of female patients enrolled was markedly lower than the number of male patients; ‡p value for incidence of rash in male versus female patients

Rash (any type) by gender after 48 weeks of treatment

Parameter	ETR + BR		Placebo + BR	
	Male (n=539)	Female (n=60)	Male (n=535)	Female (n=69)
Overall rash, %	18	30	11	9
Median onset, days	15	11.5	50	41
Median duration, days	15	14.5	26	16
Any serious AE, %	<1	0	0	0
Discontinuation, %	2	5	0	0

- No clear differences in the time to onset and duration of rash between genders in either treatment group
- Rate of discontinuation was low in both subgroups

Rash (any type) incidence by race after 48 weeks of treatment



*Asian patients excluded due to low patient numbers; local regulations in some countries prohibited the collection of ethnic information, therefore the ethnic origin of 132 patients is not included in the analysis

Grading and management of rash in the DUET trials

DAIDS toxicity grade	Definitions	Action regarding ARV medication
Grade 1 or 2	Localized rash/diffuse macular/ maculopapular or mobilliform rash/ target lesions	Continue ARV at the discretion of the investigator
Grade 3*	Diffuse rash with vesicles or bullae/ mucous ulceration	Permanently discontinue ARV medication
	Raised liver enzymes/serum sickness-like reaction/eosinophilia/fever	Refer to dermatologist
Grade 4*	Extensive bullous lesions/SJS/mucosal ulceration (two or more sites)/toxic epidermal necrolysis	Permanently discontinue ARV medication
		Refer to dermatologist

*Local safety assessment and daily follow-up for the next 5 days

- Management of rash followed generally accepted medical standards
  - cetirizine, levocetirizine, topical corticosteroids and antipruritic agents were all allowed for all grades of rash

DAIDS = Division of Acquired Immunodeficiency Syndrome

Conclusions

- Rash occurred more frequently in the ETR + BR group than in the placebo + BR group
  - 19% vs 11% (p<0.0001), respectively
  - higher incidence of rash in women than in men in the ETR group (30% vs 18%; p=0.0365); severity, however, was similar and discontinuation rate low for both genders
  - rash was maculopapular in nature and mostly emerged during the first 2 weeks of treatment
  - median duration of rash was 15 days.
- Rash was usually mild-to-moderate in severity
  - 1% grade 3 events and no grade 4 events in the ETR group.
- Rash infrequently led to treatment discontinuation
  - 2% of patients permanently discontinued.
- A history of NNRTI-related rash was not predictive of rash with ETR.
- No relationship was observed between the incidence of rash and baseline CD4 cell count or PK exposure.
- Most rashes resolved with continued treatment.

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DUET-1
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DUET-2
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