High rate of virological success in etravirine treated patients.

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Background

Etravirine is the first next-generation NNRTI that is approved for the treatment of HIV infection in patients who have experienced virologic failure while receiving an NNRTI-containing regimen. Because the drug is metabolized by cytochrome P450 isoenzymes, it cannot be co-administered with a number of other drugs , such as fosamprenavir, high-dose ritonavir, atazanavir, rifampin, and several antiepileptic medications. Etravirine demonstrates potent in vitro activity against wild-type and NNRTI-resistant strains of HIV. Several large clinical studies have documented the benefit of adding etravirine to an optimized background regimen in patients with virologic failure who are infected with multidrug-resistant HIV. The major adverse effects of etravirine therapy were reported to be nausea and rash, which are typically self-limiting and do not lead to treatment discontinuation. However, in October 2009, new safety information was released after reports of severe allergic reactions and one report of death.

Objective

Our objective was to further characterise and review adverse effects registered amongst patients treated with an etravirine (ETR) encompassing cART regimen and were monitored in the ATHENA observational cohort in the Netherlands.

Methods

Study population:

All HIV infected patients, monitored in one of the Netherlands HIV Treatment Centres who were 18 years or older and ever initiated ETR were selected for his study.

Statistical analysis

Kaplan Meier estimates on the probability of ETR discontinuation were plotted.

Resistance

Resistance to antiretroviral drugs was determined by analyses of HIV RT and protease gene sequences using the Stanford algorithm for scoring resistance associated mutations.

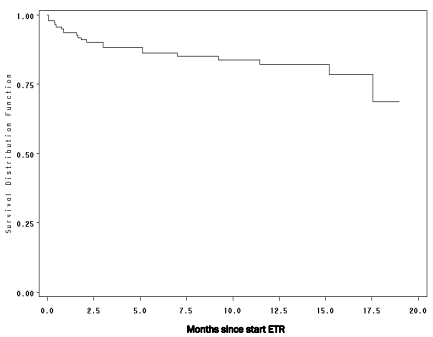

Figure 1: Kaplan Meier estimates of the proportion of patients who remain on ETR treatment.

Results (Figure 1)

- 12 months after the start of ETR, 82% of the patients were still on ETR encompassing cART (95%CI: 73-88%).
- Treatment with ETR was discontinued in 22 patients:
  - in 10 patients for reasons of toxicity
  - In 4 patients because of rash. All rashes occurred in patients with CD4 cell counts>200 cells/mm3 at ETR initiation
  - In 3 patients because of dermatitis or itchiness
  - In 3 patients for other reasons

Table 1: Demographic characteristics of 151 patients on ETR

	N(%)
Gender	
-Men	132 (87)
-Women	19 (13)
Age in years at time of ETR start (median, IQR)	48 (43-56)
Earlier cART	148 (98)
Year of HIV diagnosis	
<1996	119 (78)
1996-2000	20 (13)
2001-2007	12 (8)
Year of start cART	
<1998	120 (79)
1998-2002	18 (12)
2003-2009	13 (9)
NRTI backbone	
No NRTI	49 (32)
TDF+FTC	11 (7)
AZT+3TC+TDF	37 (24)
other	54 (36)

Results (Table 1)

151 patients initiated ETR between january 2006 and June 2009. The most common reasons for switch to ETR were toxicity (22%) and failure (38%) on earlier treatment.

Table 2: Clinical characteristics of patients on ETR

Last CD4 count before start ETR	286 (190-460)
Number of pt with adverse events while CD4 count at start ETR<200	14/54 (26)
Number of pt with adverse events while CD4 start ETR>=200	15/97 (15)
Deaths cd4 count at start ETR<200	8/54 (17)
Deaths cd4 count at start ETR>=200	0/97 (0)
Last HIV RNA plasma level before start (median, IQR) CD4<200 CD4>=200	17842 (3830-71368) 761 (49-13456))
HIV RNA plasma level 6 months after start (median, IQR) CD4 at start <200 CD4 at start>=200	50 (40-76) 40 (40-50)

Results (Table 2):

- Median viral load at ETR initiation was lower in patients with CD4 cell count>200 at time of ETR initiation compared to those with CD4 cell counts<=200
- Within 6 months of ETR treatment 76% of all patients achieved HIV RNA plasma levels <=1.7 $\log_{10}$copies/ml

Table 3: Number of patients treated with ETR with evidence of resistance to specific ARV drugs, according to the Stanford algorithm for scoring mutations.

		Reistance level N (%)			
	N Tested	Potentially low	Low-level	Intermediate	High-level
PI					
fAPV	127	5(4)	11(9)	37(29)	38(30)
IDV	127	3(2)	6(5)	23 (18)	62(49)
ATV	127	3(2)	12(9)	37(29)	46(36)
NFV	127	3(2)	1(1)	10(8)	87 (69)
SQV	127	8(6)	7(6)	31(24)	50(40)
TPV	127	6(5)	22(17)	50(39)	13(10)
DRV	127	12(9)	39(31)	32 (25)	2 (2)
NRTI					
dTC	126	3(2)	12(10)	2(2)	90(71)
FTC	126	3 (2)	12(10)	2(2)	90(71)
ABC	126	5(4)	9(7)	36(29)	61(48)
AZT	126	1(1)	7(6)	32(25)	65(52)
D4T	126	5(4)	10(8)	34(27)	61(48)
DdI	126	2 (2)	8 (6)	38 (30)	59 (47)
TDF	126	9(7)	18(14)	70(56)	3(2)
NNRTI					
NVP	126	8(6)	0	1(1)	73(58)
ETR	126	14(11)	18(14)	38(30)	4(3)
EFV	126	3 (2)	8(6)	9(7)	57(45)

Conclusions

No life-threatening side effects were reported. Rash only occurred in patients with high CD4 cell counts suggesting that the risk of hypersensitivity reactions due to ETR is highest in patients with high CD4 cell counts. In patients with less treatment options, ETR seems a safe option resulting in a high rate of virological success.