

Immunological Success is Predicted by Enfuvirtide but not Interleukin-2 in Immunocompromised Patients, Final Results of the ANRS 123 ETOILE Randomized Trial



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BACKGROUND AND OBJECTIVES

The effect of Interleukin-2 (IL-2) in patients with low CD4 counts and multiple treatment failure is unknown.
The ANRS 123 ETOILE trial was designed to evaluate the efficacy and safety of adding IL-2 to an optimized background treatment (OBT) in immunocompromised patients presenting virological failure and no treatment options.

METHODS

Study design : multicentric, national, open-label randomized controlled trial.
Eligibility criteria : age ≥ 18, written informed consent, HIV-1 infected patients, at least 2 CD4 values ≤ 200/mm³ (one at baseline and one in the last 6 months), HIV-1 RNA ≥ 10000 copies/ml, genotypic score (GS) based on all available genotypic results showing ≤ 2 active drugs (according to ANRS algorithm).

Treatment : patients were randomized into 2 arms :
- **IL-2 + OBT :** 8 subcutaneous IL-2 cycles (4.5 MUI twice daily, 5 days, from Week 2 to Week 42) + OBT (from Week 0 to week 96)
- **OBT* alone :** OBT alone (from Wk 0 to Wk 96)

* **Optimized background treatment** was chosen by investigator before randomization: protocol recommended to use active drugs on GS and enfuvirtide (T20) in T20-naïve patients.

Treatment considered as optimized if : use (during ≥ 24 weeks from Wk 0) of enfuvirtide in T20-naïve patients, use of an active drug according to GS or use of tipranavir (not in GS, only if active according to screening genotype result).

Primary outcome measure : proportion of patients with a CD4 count ≥ 200/mm³ at Wk 52.

Secondary outcome measures : proportion of patients with a CD4 count increase ≥ 50/mm³ from Wk 0 to Wk 52, median HIV-1 RNA, HIV related events and tolerance.

Analysis : Intent to treat (missing=failure); proportions compared using chi-square or Fisher exact tests; univariate logistic regression including baseline data and optimization characteristics; variables with a p-value ≤ 0.25 were included in the multivariate analysis.

Figure 1 : Design of the ANRS 123 ETOILE trial



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RESULTS

From June 2004 to December 2005, 56 patients were randomized : 28 in the IL-2 + OBT group and 28 in the OBT alone group.
At study entry, patients had advanced HIV disease : 2/3 has already reached the AIDS stage, were severely immunocompromised (median CD4 count 64/mm³), had high viral load (median : 4.9 log₁₀ copies/ml) and 43% had a GS = 0 (Table 1).

Background treatment regimen could be optimized in 23 patients (41%) : with T20 only (n=6), with 1 or 2 other active drug(s) according to GS (n=7) or with T20 plus 1 or 2 other active drugs (n=10). Treatment could be not optimized in 33 patients (59%).

IL-2 : 15 patients did not complete their 8 IL-2 cycles (including 2 having only 1 cycle). Reasons for IL-2 interruption were : failure (n=8), serious adverse events (SAE) (n=3, see below), patient's decision (n=3) and investigator's decision (n=1).

CD4 count : 4 patients (14%) in the IL-2 + OBT and 5 (18%) in the OBT alone group reached the primary outcome of CD4 ≥ 200/mm³ at Wk 52 (p=1.0), 7 patients (25%) in the IL-2 + OBT and 9 (32%) in the OBT alone group experienced a CD4 increase ≥ 50 CD4 cells/mm³ from Wk 0 to Wk 52 (p=0.5). CD4 trends from Wk 0 to Wk 52 according to IL-2 and T20 optimization are presented on Figure 2.

HIV-1 RNA : median values at Wk 52 were 4.5 log₁₀ copies/ml for IL-2 + OBT vs. 4.6 for OBT alone (Wilcoxon test, p=0.08).
In multivariate analysis, optimization with T20 (with or without other active drugs on GS) was associated with immunological success.

Primary outcome was reached by 50% of patients with T20 vs. 2.5% without T20 (adjusted OR 49.3 [1.7-999], p=0.02); secondary outcome was reached by 75 % of patients with T20 vs. 10% (adjusted OR 36 [3.7-349], p=0.002) (Table 2).

AIDS events and safety : 8/28 (29%) patients in the IL-2 + OBT group and 6/28 (21%) in the OBT alone group presented AIDS-defining events (p=0.7) (Table 3).

29 SAE occurred in 16 IL-2 + OBT patients and 20 in 13 patients of OBT alone group. 43/49 SAE were hospitalizations and 6 grade 4 events (none related to trial treatments). Only 3 SAE were considered as possibly related to IL-2 (1 acute renal failure, related to ARV and IL-2 and 2 lymphomas occurring in profoundly immunosuppressed patients). 8 SAE were related to antiretroviral drugs (nevirapine toxidermia, myocardial ischemia, hepatitis, pneumopathy, osteonecrosis, jaw osteitis, cryptosporidiosis and hematoma in muscle). 5 patients died (2 with lymphoma and 3 with pneumonia and sepsis).

Table 2 : Univariate and multivariate models results, ANRS 123 ETOILE trial

	Primary endpoint % patients with CD4 ≥ 200/mm ³ at Wk52				Secondary endpoint % patients with CD4 increase ≥ 50/mm ³ Wk0- Wk52			
	Univariate analysis OR [95% CI]	p	Multivariate analysis OR [95% CI]	p	Univariate analysis OR [95% CI]	p	Multivariate analysis OR [95% CI]	p
Group : IL-2 + OBT vs OBT alone	0.8 [0.2-3.2]	0.72			0.7 [0.2-2.3]	0.55		
Baseline CD4 count : ≥ 100 vs < 100/mm ³	13.0 [2.3-72.3]	0.004	35.2 [1.6-757]	0.02	2.3 [0.7-7.9]	0.17	1.4 [0.2-8.9]	0.69
Baseline HIV-1 RNA (per 1 log ₁₀ copies/ml)	3.1 [0.7-13.3]	0.13	1.6 [0.2-16]	0.69	2.6 [0.8-8.1]	0.10	3.6 [0.7-19.0]	0.13
CDC stage C at entry (vs A or B)	0.8 [0.2-3.3]	0.73			1.1 [0.3-3.7]	0.86		
Delay from 1st HIV diagnosis (per year)	0.7 [0.6-0.9]	0.02	1.0 [0.6-1.6]	0.95	0.8 [0.7-1.0]	0.02	1.1 [0.8-1.5]	0.48
OBT with active drug in GS alone (yes vs no)	0.9 [0.1-8.1]	0.89			0.4 [0.04-3.4]	0.39		
OBT with T20 +/- active drug (yes vs no)	39.0 [4.3-357]	0.001	49.3 [1.7-999]	0.02	27.0 [5.8-125]	<0.0001	36.0 [3.7-349]	0.002

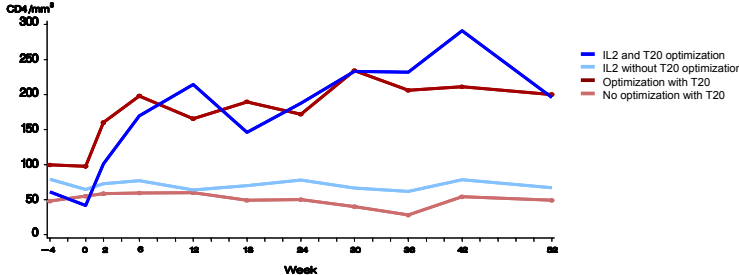
Table 1 : Baseline characteristics, ANRS 123 ETOILE trial

Group	IL-2 + OBT	OBT alone
N	28	28
Gender, n (%)	male 25 (89)	25 (89)
Age (years)	mean (SD) 44 (9)	48 (8)
HIV risk factors, n (%)	homo-bisexual 11 (39)	16 (57)
	heterosexual 9 (32)	8 (29)
	transfusion-hemophilia 4 (14)	0 (0)
	intravenous drug use 1 (4)	2 (7)
	homo + IV drug use 1 (4)	1 (4)
	unknown 2 (7)	1 (4)
Delay from 1st HIV diagnosis to study entry	median delay in years (min-max) 12 (8-22)	14 (7-19)
CDC disease stage, n (%)	A 6 (21)	4 (14)
	B 6 (21)	6 (21)
	C 16 (57)	18 (64)
CD4 count (cells/mm³)	mean (IQR) 53 (9-108)	68 (25-120)
	mean (SD) 72 (70)	77 (61)
HIV-1 RNA (log₁₀ copies/ml)	median (IQR) 5.0 (4.4-5.4)	4.9 (4.5-5.1)
	mean (SD) 4.9 (0.6)	4.9 (0.6)
Genotypic score (GS), n (%)	0 13 (46)	11 (39)
	1 or 2 15 (54)	17 (61)

Table 3 : AIDS defining events (n), ANRS 123 ETOILE trial

Group	IL-2 + OBT		OBT alone	
	N=28	N=28	N=28	N=28
Cytomegalovirus infections	1	4		
Oesophageal candidiasis	2	2		
Pneumonia	1	4		
Cryptosporidiosis	2	1		
Cryptococcosis		2		
Lymphoma	2			
Cachexia	1	1		
Mycobacterial infection				
Kaposi sarcoma			1	
PMML	1			
Total	10	15		
% pts with at least one AIDS defining event	8 (29%)	6 (21%)		p=0.7

Figure 2 : CD4 count according to IL-2 and T20 optimization, ANRS 123 ETOILE trial



CONCLUSIONS

In this trial, conducted in severely immunocompromised patients with limited treatment options and ongoing viral replication, IL-2 globally failed to increase CD4 cells and incidence of AIDS complications. Interestingly, the use of enfuvirtide, even on an otherwise poorly optimized background regimen, was highly associated with immunological success at week 52, either in terms of CD4 counts ≥ 200/mm³ or in terms of CD4 increase ≥ 50/mm³. These results emphasize the importance of prescribing a new drug family in salvage therapy.

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