

RESPONSE TO IL-2 IN PATIENTS WITH IMMUNODISCORDANT RESPONSE TO HAART IS ASSOCIATED WITH LONG-TERM CLINICAL BENEFIT

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BACKGROUND AND OBJECTIVE

> Around 5% of HIV-infected patients who start HAART have an immunological discordant response (IDR) with no increase in CD4 cells count in spite of undetectable viral load.

> Different observational cohorts showed that patients with IDR to HAART have a higher risk for AIDS related complications than complete responders patients.

> In HIV-1 infected patients Interleukine-2 (IL-2) has been associated with analytical benefit with significant increase in CD4 cell counts. However, this increase has not yet been linked to a clinical benefit.

> Currently there are two ongoing studies (ESPRIT and SILCAAT) testing the hypothesis that treatment with IL-2 is associated with clinical benefit in the long-term follow-up.

> We reviewed long-term clinical evolution of patients with IDR to HAART who have been treated with IL-2 in our institution.

METHODS

Inclusion criteria

- HIV-1 infected patients under HAART during the last 12 months with IDR to treatment, and who started treatment with CD4 cells count < 200 cells/μL
- CD4 cells count < 250 cells/μL at the beginning with IL-2 treatment
- Immunological discordance response defined by:
 - No significant increase of CD4 cells count over baseline
 - Plasma viral load < 50 copies/mL for at least 6 months

Exclusion criteria

- Treatment with steroids, chemotherapy or other immunotherapy drugs
 - Patients with autoimmune disorders such as psoriasis, lupus,...
- Study period:** 2000-2007
- IL-2 treatment**
- Patients were planned to receive cycles of IL-2 every 8 weeks for at least 3 cycles
 - Dose of IL-2: 4.5-7.5 x 10⁶ UI BID for 5 days
 - Ibuprofen and/or acetaminophen were administered in order to avoid IL-2 adverse effects

Response criteria

- In patients with CD4 baseline > 100 cells/μL, response to IL-2 was defined as an increase of 50% above those of the baseline
- In patients who started IL-2 below 100 cells/μL, response was defined as an increase of 50 absolute cells

End-points: death for any cause or AIDS-defining event

RESULTS

> During study period 119 HIV-1 infected patients received IL-2 in our Institution.

> 93 of them meet inclusion criteria

> 56 patients (60.2 %) were considered as responders and 37 (39.8 %) as non-responders.

> Baseline clinical and analytical characteristics are summarized in **Table I**

> Median IL-2 per dose was 4,5 x 10⁶ UI, and median IL-2 cycles administered were 6 (IQR 4-6) in responders vs 5 (IQR 3-6) in non-responders

> Regarding to immunological response, the differences between groups are showed in **Figure I**

> After IL-2 treatment, median follow-up was 33 months (IQR 11,2-54,7) in responders versus 36 months (IQR 5,5-58) (p=0,85)

Table I. Baseline clinical and analytical characteristics. No significant differences were assessed between responders and non-responders.

* Data are in median (IQR)

	All Patients n=93	Responders n=56	Non-responders n=37	p
Gender men (%) / women (%)	77 (82,8) / 16 (17,2)	46 (82,1) / 10 (17,9)	31 (83,8) / 6 (16,2)	0,5
Age*	41 (37-45)	41 (35-44)	43 (38-47)	0,1
CDC score N (%)				0,6
C3	61 (65,3)	35 (62,5)	26 (70,3)	
B3	9 (9,7)	6 (10,7)	3 (8,1)	
A3	22 (23,7)	15 (26,8)	7 (18,9)	
HIV infection (years)*	6 (2-11,5)	5,5 (2-11)	7 (2-12,5)	0,2
Risk group N (%)				0,18
IDU	46 (49,5)	26 (46,4)	20 (54,1)	
Homosexual	17 (18,3)	11 (19,6)	6 (16,2)	
Heterosexual	23 (24,7)	15 (26,8)	8 (21,6)	
Other	7 (7,5)	4 (7,2)	3 (8,1)	
Months on HAART*	33 (18-80)	30,5 (15,2-59)	43 (19-102)	0,29
Nadir CD4 cell/mm ³ *	40 (14,2-77,7)	44 (24-86)	31 (7-71)	0,07
Baseline CD4 cell/mm ³ *	165 (110-195)	157 (108-192)	169 (168-205)	0,16
Hepatitis Coinfection N (%)				0,08
HCV coinfection	51 (54,8)	27 (48,2)	24 (64,9)	
HBV coinfection	9 (9,7)	4 (7,1)	5 (13,5)	0,3

Figure I. CD4 evolution in non-responders and responders at months 12 and 6 before beginning IL-2, at baseline, at 2 and 6 months after IL-2, and last known value (p<0,001)

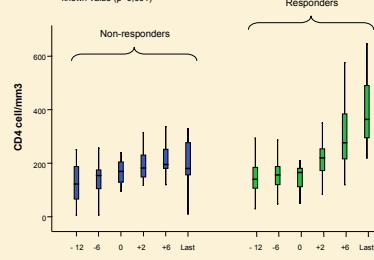
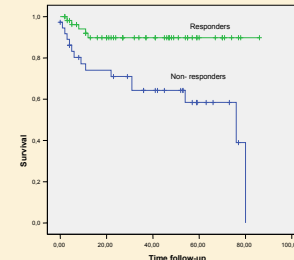


Figure II. Survival analysis (Kaplan-Meier). AIDS defining event and/or death by any cause.



> During follow-up a total of 20 patients suffered an AIDS defining event and/or death for any cause, 15 of them were non-responders (40,5 %) and 5 were responders (8,9 %) (p< 0,001). **Table II**

* Regarding deaths for any cause, there were 11 deaths (30,6 %) in non-responders and 5 in responders (p=0,01).

* Considering AIDS defining events, we observed 7 (24,1%) events in non-responders (4 of them died) and 1 (2%) who died in responders, p=0,003

> In Kaplan-Meier survival analysis, we assessed a statistically significant higher AIDS defining event or death for any cause in non-responders group versus responders (Log-Rank=0,001). **Figure II**

> In a multivariate Cox's model no response to IL-2 was significantly associated with increase of death for any cause or AIDS-defining events (hazard ratio 4,6; CI95% 1,6-12,7) p=0,003

Events	Death	No Death
Non responders		
Mycobacterium avium	2	0
Visceral leishmaniasis	2	2
Cryptococcal meningitis	0	1
Hepatocellular carcinoma	2	0
HCV cirrhosis	1	0
Anal carcinoma	1	0
Disseminated listeria infection	1	0
Urinary sepsis	1	0
Subarachnoid bleeding	1	0
Status epilepticus	1	0
Responders		
B lymphoma	1	0
Community acquired pneumonia	1	0
Gastroenteritis	1	0
Myocarditis	1	0
Lactic acidosis	1	0

Table II. New AIDS defining event or any death for any cause during follow-up in responders and non-responders

CONCLUSIONS

In patients with CD4 < 250 cells/μL and an immunological discordant response to HAART, response to treatment with IL-2 is associated with a clinical benefit.

IL-2 should be offered to all patients with an immunological discordant response to HAART and a CD4 cell counts < 250 cells/μL.