

Interleukin-2 (IL-2) as treatment for immunological discordant patients with CD4 below 200 cells/ μ L after at least one year of HAART (GESIDA 33/03 Study).

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INTRODUCTION

- In spite of the use of highly active antiretroviral treatment (HAART), around 10-15% of patients that start treatment below 200 CD4+ T cells/ μ L will never increase these over 200, even in presence of a good control of virological replication. These patients, called immunologic discordant (ID), have a higher risk to develop opportunistic infections or die during the following years than patients with a normal immune reconstitution.
- Interleukin 2 (IL-2) is a T-cell derived cytokine that induces the activation, proliferation and differentiation of T, B, and NK cells. It is approved for treatment of metastatic renal cell carcinoma and for some types of melanoma. When administered by intermittent subcutaneous injection it induces an expansion of the CD4+ T cells, especially those of naive phenotype. These increases in the CD4+ T cells lead to it in HIV-1 infected patients. When IL-2 is administered to these patients it produces a progressive increase in the number of peripheral CD4+ T cells. Based on these facts, although it is not commercialized yet, in Spain it is possible to use IL-2 for treatment of HIV-infected patients as a compassionate use.
- In this work we presented the Spanish experience on the use of IL-2 in ID patients.

METHODS

- The Gesida 33/03 study enrolls all patients with an approved compassionate use of IL-2 in Spain

Inclusion criteria

1. Documented HIV-1 infection
2. Age > 18 years
3. At least 12 months of HAART
4. Undetectable viral load for at least 24 weeks or a VL < 5.000 copies/mL for at least 24 weeks in patients with few therapeutic options.
5. CD4+ T cells counts < 200/ μ L without significant increase during the last 24 weeks.
6. Authorization from Spanish Health Authorities to use IL-2 as a compassionate use

IL-2 administration

- Patients were treated with IL-2 (Macrolin, Chiron Europe) twice daily as subcutaneous injections of 4.5 MIU for 5 days. After 7 weeks IL-2 cycle was repeated with the same schedule as before.
- Patients were clinical and analytically evaluated on day one of every cycle before the first dose of the following cycle. That's why the response of CD4+ cell counts for every cycle was performed on the first day of the following cycle. Most of the patients were treated in outpatient clinic, and they were instructed to register all events happening during the IL-2 treatment in a special sheet designed for it.
- All patients were instructed to take ibuprophen and acetaminophen during the cycle beginning immediately before the first dose of IL-2.
- To be evaluated for efficacy patients were required to receive at least 3 cycles of IL-2.

Response to IL-2

- Patients was considered as responder to IL-2 in the presence of:
 - An increase of at least 50 CD4+ cells/ μ L in patients with baseline CD4+ cell counts < 100 cells/ μ L or
 - An increase of at least 50% in the baseline CD4+ cell counts for patients with baseline CD4+ cell counts > 100 cells/ μ L.

RESULTS

- Between May 2003 and December 2004, 137 patients were included in the study. Main clinical and epidemiological characteristics at baseline are shown in Table I. At present 92 patients have completed 3 IL-2 cycles, 10 discontinued due to adverse effects during the first three cycles and 35 are still receiving their first 3 cycles of IL-2.
- There were no differences in the median amount of IL-2 administered by cycle (Figure 1). Overall the adverse effects were more frequent during the first 2 cycles, specially those considered as grade III-IV (Figures 2 and 3). However, most of the AE disappeared 24 hours after finalization of the cycle (Table 2).
- For those patients who completed 3 cycles of IL-2 there was a significant increase (from 133 to 192 cells/ μ L, $p < 0.05$) in the absolute number of CD4+ cell counts between baseline and the end of cycle-3, as well as in the CD4+ percentage (from 11% to 14.5%, $p < 0.05$), and 42% of them increase their CD4+ cell counts from below 200 to above this figure.
- There were no differences in the number of CD8+ cell counts from baseline to cycle-3 (635 vs 690 cells/ μ L, $p > 0.05$), nor in the number of patients with an undetectable viral load (93.5% at baseline vs 89.6% after the 3rd cycle, $p > 0.05$).
- After the first cycle 26.8% of patients were considered as responders to IL-2, 28.7% after cycle-2, and 43.2% after cycle-3. For those patients not responding to IL-2 after 3 cycles, 10% of them were considered as responders in cycles 4 or 5 (Figure 4).
- Four patients developed an opportunistic disease during the follow-up: Kaposi's Sarcoma, CMV retinitis, possible PCP, and disseminated tuberculosis. One patient dye after 3 cycles of IL-2 because acute cholecystitis.
- We couldn't identified any predictor factors for response to IL-2. However, females (23,1% vs 46,7%, $p = 0,09$), and a BMI > 20 (37% vs 66,7%, $p = 0,064$) were associated with a poorer CD4+ response.

Table I. Main clinical and epidemiological characteristics

Males	83%
Age	41,1 years (37-46)
Weight	66 Kg (58 - 74)
HIV risk practice	
IVDU	52,3%
Sexual	40,4%
Others	3,8%
Unknown	3,8%
CDC Category "C"	68,7%
Hepatitis virus coinfection	
Hbs + Ag	15%
HCV +	59,8%
Naïve CD4+	31 (9-54)
Undetectable viral load	93,5%
Baseline CD4+	135 (86-177)
Previous Opportunistic infections	134 episodes
OI Prophylaxis	91,6%
First HAART therapy	24,1%
Second HAART therapy	18,9%
Rescue therapy	57%
Most frequent HAART	13,9%
AZI + 3TC + EFV	5,1%
DTT + 3TC + LOP/r	4,4%
3TC + TDF + EFV	4,4%
d4T + 3TC + NFV	4,4%
3TC + TDF + LOP/r	4,4%

Figure 1. Median amount of IL-2 administered per cycle (MIU)

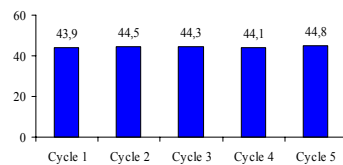


Figure 2. Patients with AE (%)

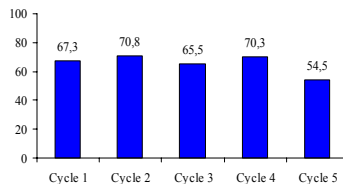


Figure 3. Patients with AE Grade III-IV (%)

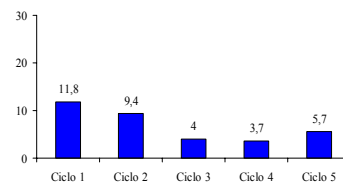


Table II. Most frequent AE during first 3 cycles

	Cycle 1	Cycle 2	Cycle 3
Fever	67.3	69.3	65.5
Malaise	35.7	41.3	39.3
SC nodules	26.5	26.5	9.8
Nausea/vomiting	19.3	19.3	11.4
Rash	11.2	11.2	3.2

CONCLUSIONS

- IL-2 may increase CD4 counts even in HIV-infected patients with severe immunocompromise, and should be considered in patients with immunovirological discordant response to HAART and CD4 counts < 200/ μ L.
- Some patients may have a slow response to IL-2 with increase of the CD4+ cell counts beyond the 3rd cycle.
- Although the occurrence of adverse effects is frequent, and only 10% discontinue IL-2 therapy for this reason, they disappeared quickly after the finalization of the cycle.
- Grade III-IV adverse effects occur in less than 15% of patients, and were more common during the first cycles.

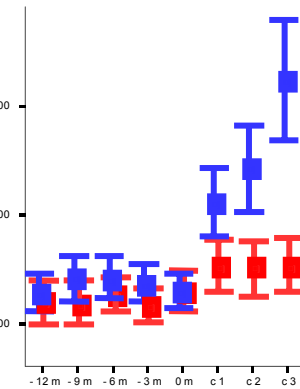


Figure 4. Mean increase of CD4+ in responder (blue) and non-responder (red)

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