

Interleukin-2 (IL-2) in Conjunction with HAART in Early HIV-1 Infection Increases

Naïve and Memory CD4 Cells and Lowers Activation Markers

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Abstract

BACKGROUND: We examined immunologic and virologic markers when IL-2 was added to HAART in the treatment of early HIV-1 infection. **METHODS:** Subjects started Combivir + nelfinavir or other HAART within 12 months of HIV-1 infection. Once HIV-1 RNA was < 500 copies/mL, subjects were randomized to add IL-2 immediately or delayed by 48 weeks. IL-2 was administered 7.5 million units SQ BID for 5 days every 8 weeks for 6 cycles. HIV-1 RNA was quantitated by bDNA 3.0 (Bayer), and flow cytometry was performed to measure CD4 naïve (RA+) and memory (RO+) cells and CD4 and CD8 activation (CD38+). **RESULTS:** Of 62 subjects, 29 were randomized to early IL-2 and 33 to delayed IL-2. To date, 31 subjects have completed all 6 cycles of IL-2 [19 in the early IL-2 group and 12 in the delayed IL-2 group]. There were no baseline differences between groups in age, gender, ethnicity, HIV risk factors, time to initiation of HAART, CD4 count, HIV-1 RNA, or CD4/CD8 activation. From randomization to week-48, median CD4 cell activation (CD38+) declined from 38.9 mean fluorescent intensity units (IQ range, 15.0 – 57.8) to 5.5 (2.6 – 7.1) in the early IL-2 group, and from 38.1 (23.3 – 43.7) to 19.0 (7.1 – 29.5) in the delayed IL-2 group (difference between groups, P=0.008). Median CD8 cell activation (CD38+) declined from 52.8 (25.0 – 98.7) to 1.0 (1.0 – 5.1) in the early IL-2 group, and from 115 (59.5 – 257) to 3.7 (1.0 – 14.3) in the delayed IL-2 group (difference between groups, P=0.12). Comparing baseline to week-12 of IL-2, the mean change in the percentage of naïve (RA+) and memory (RO+) CD4 cells was +2.1% (range -17 to +16) and +0.8% (-18 to +17), respectively. 48 weeks after starting IL-2, median CD4 count increased from 645 cells/mL (IQ range, 520 – 918) to 1326 (945 – 2142) in the early IL-2 group and from 629 (540 – 714) to 1431 (1160 – 1771) in the delayed IL-2 group (difference between groups, P=0.81), and HIV-1 RNA was < 50 copies/mL in 79% and 92% of subjects in the early and delayed IL-2 groups, respectively (P=0.62). **CONCLUSIONS:** Subjects exhibited a similar rise in CD4 cell count with no loss of HIV-1 suppression when IL-2 was added to HAART in early HIV-1 infection, whether IL-2 was initiated immediately after viral suppression or delayed by 48 weeks. Naïve and memory CD4 cells were increased proportions similar to baseline after IL-2 administration. CD4/CD8 cell activation declined on HAART with or without IL-2. CD4 cell activation declined to a greater extent when IL-2 was co-administered.

Introduction

IL-2 has been shown to increase both naïve and memory CD4 cell counts in individuals chronically infected with HIV when used in conjunction with suppressive antiretroviral therapy.

We examined immunologic and virologic parameters when IL-2 was added to HAART in the treatment of early HIV infection.

Methods

Subjects were identified as being recently HIV-1 infected by one of the following methods:

- Documented negative HIV-1 antibody test within 12 months, or
- Detectable HIV-1 RNA in the absence of HIV-1 antibody, or
- Unreactive detuned HIV-1 antibody with a positive ELISA and history consistent with recent HIV-1 infection.

Subjects initiated Combivir + nelfinavir or other HAART regimen within 12 months of being HIV-1 infected.

Once HIV-1 viral load was < 500 copies/mL, subjects were randomized to receive IL-2 beginning immediately or delayed by 48 weeks.

IL-2 was administered 7.5 million units SQ BID for 5 days every 8 weeks for 6 cycles.

HIV-1 RNA was quantitated by bDNA 3.0 (Bayer).

Flow cytometry was performed to measure CD4 naïve (RA+) and memory (RO+) cells and CD4 and CD8 activation (CD38+).

Results

Table 1.

Pre-HAART Baseline Characteristics			
	Early IL-2 (N=29)	Delayed IL-2 (N=33)	P-value
Age (years)*	34 (30-40)	32 (29-39)	0.61
Male (%)	93	97	0.60
Caucasian (%)	76	70	0.77
MSM (%)	93	97	0.82
IVDU (%)	14	3	0.17
Time from infection to start HAART (%)			
0-6 mo	86	94	0.36
6-12 mo	14	6	
CD4+ (cells/mL)*	490 (364-680)	448 (374-612)	0.70
CD8+ (cells/mL)*	768 (574-1075)	800 (544-1020)	0.93
CD4+38+ (mean fluorescent units)*	39 (15-58)	38 (23-44)	0.83
Log HIV viral load*	4.76 (3.49-5.36)	4.95 (4.27-5.35)	0.56

* reported as median (Interquartile range)

Subject baseline characteristics are listed in Table 1. During the first 48 weeks, when subjects randomized to delayed IL-2 were receiving HAART only, the effect of HAART with or without IL-2 on activation markers can be seen in Table 2.

Table 2.

Effect of HAART +/- IL-2 on Activation State			
	Early IL-2 (IL-2 + HAART) (N=17)	Delayed IL-2 (HAART only) (N=16)	P-value (difference between groups)
CD4+ CD38+ *			
Week 0	38.9 (15.0-57.8)	38.1 (23.3-43.7)	0.008
Week 48	5.5 (2.6-7.1)	19.0 (7.1-29.5)	
CD8+ CD38+ *			
Week 0	52.8 (25.0-97.7)	115 (59.5-257)	0.12
Week 48	1.0 (1.0-5.1)	3.7 (1.0-14.3)	

* reported as median fluorescent intensity units (Interquartile range)

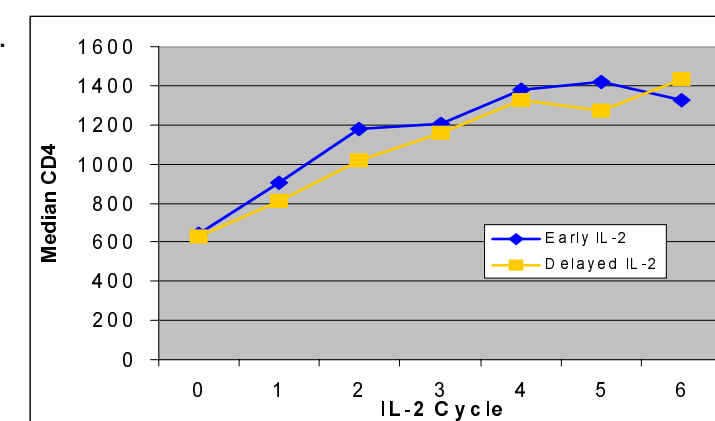
By looking at subjects with 48 weeks of follow up after starting IL-2, the overall effect on CD4 cell count and viral load by treatment arm (Table 3) and the effect on CD4 cell count by number of IL-2 cycles completed (Figure 1) can be seen.

Table 3.

Effect of Early vs. Late IL-2 on CD4 and viral load			
	Early IL-2 (N=19)	Delayed IL-2 (N=12)	P-value
CD4 at Week-0 of IL-2*	645 (520-918)	629 (540-714)	0.31
CD4 at Week-48 of IL-2*	1326 (945-2142)	1431 (1159-1171)	0.81
HIV viral load < 50 copies/mL after 6 cycles of IL-2 (%)	79	92	0.62

* reported as median cells/mL (Interquartile range)

Figure 1.



Grouping all subjects for whom data is available, the effect of IL-2 on naïve and memory CD4 cell phenotype is shown in Table 4.

Table 4.

Effect of IL-2 on Naïve and Memory CD4 Subsets (N=12)			
	Baseline	After 2 cycles IL-2	Change
CD4+ RA+ (Naïve)*	35 +/-10	37 +/-12	+2.1 +/-10
CD4+ RO+ (Memory)*	63 +/-12	64 +/-11	+0.8 +/-9

* reported as mean percent (+/- SD)

Conclusions

The addition of IL-2 to HAART in early HIV infection results in similar changes in CD4 cell count whether initiated immediately upon viral suppression or delayed by 48 weeks.

IL-2 can be administered to individuals on HAART without loss of viral suppression.

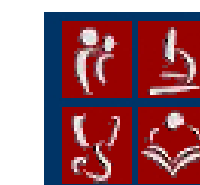
Naïve and memory CD4 cells were increased in proportions similar to baseline after 2 cycles of IL-2.

CD4+CD38+ and CD8+CD38+ levels declined on HAART with or without IL-2; however, CD4+CD38+ levels declined to a greater extent when IL-2 was co-administered.

When administered in early HIV infection, IL-2 may lead to an expansion of both naïve and memory CD4 pools, which in the presence of HAART maintain a low activation state.



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