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Repeated Injections of r-hIL-7 in HIV Patients Receiving cART in INSPIRE 2 & 3 Phase II Trials

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Background

Phase I/II studies in HIV-infected patients receiving cART have shown that administration of 3 weekly subcutaneous (s/c) injections of Recombinant Human Interleukin 7 (r-hIL-7) is safe and increase numbers of both naive and memory CD4 and CD8 T cells. Here, we report the pooled data from two phase II trials evaluating the effect of repeated cycles of r-hIL-7 with the objective of restoring and maintaining CD4$^+$ T cell count over 500 cells/μL.

r-hIL-7 treatment

- **Product:** CYT107 - Purified glycosylated 152 amino acid recombinant human Interleukin-7
- **Mode of administration:** A cycle = 3 weekly subcutaneous injections of CYT107 at the dose of 20 μg/kg
- **Intervention:** Subjects received a first "induction" cycle and they were eligible to receive new "maintenance" cycles if the CD4+ T cell count falls below 550 Cells/μL when monitored at quarterly visit (every 3 months)
- **Primary biological activity end-point:** Restoration and maintenance of CD4+ T cell count>500 cells/μL

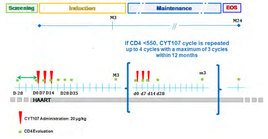
INSPIRE 2

- Single arm clinical trial conducted in US and Canada
- 23 included HIV-1-infected patients under cART for at least 12 months
- HIVRNA<50 cp/ml and CD4$^+$ T-cells count $\in$ [100-400] cells/μL
- 2 years of follow up with a maximum of 4 cycles within 21 months and 3 cycles within 12 months

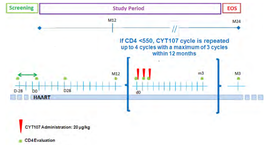
INSPIRE 3

- Double arm clinical trial conducted in Italy, Switzerland and South Africa
- 92 randomized HIV-1-infected patients under cART for at least 24 months
- HIVRNA<50 cp/ml and CD4$^+$ T cell count $\in$ [100-350] cells/μL
- 2 years of follow up with a maximum of 4 cycles within 21 months and 3 cycles within 12 months
- *Control arm*: Subjects received r-hIL-7 only after 12 months of follow up if their CD4$^+$ count still below 500 cells/μL

INSPIRE 2 & CYT107 arm INSPIRE 3



Control arm INSPIRE 3

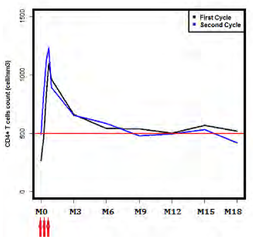


Patients characteristics

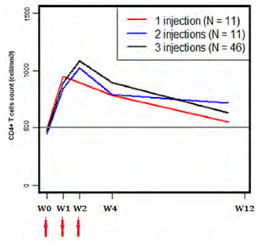
Characteristic: Median (Q1,Q3)	INSPIRE 2	INSPIRE 3
Number of patients included	23	88
Age (years)	47 (42,51)	43 (37,51)
Female (%)	13.1 %	34.1%
Ethnic origin (Cauc/Afr/Other)	(16/3/4)	(39/46/3)
Time since HIV diagnosis	8 (4,20)	6 (3,13)
Duration of ARV	5 (4,16)	4 (3,6)
Stage at diagnosis (A/B/C)	(12/2/9)	(38/11/39)
CD4$^+$ T cell count (cells/μL)	263 (191,320)	266 (215,326)
CD8$^+$ T cell count (cells/μL)	604 (405,867)	633 (457,843)
CD4$^+$ T cell count nadir	41 (19,163)	54 (19,126)
CD4$^+$/CD8$^+$ ratio	0.48 (0.27,0.59)	0.42 (0.29,0.56)
Proviral HIVDNA, $\log_{10}$ cp/10^6 CD4$^+$	2.46 (2.16,3.28)	3.12 (2.24,3.58)
Number of treated patients	23	84
Months of follow up	23 (22,24)	22 (20,23)
Months between cycles	12 (6,12)	6 (6,9)
Injections received	5 (3,6)	5 (3,6)
Number of started cycles	1 (1,2)	1 (1,2)
Number of cycles completed	2 (1.5,2)	2 (1,2)

CD4$^+$ T cell dynamics

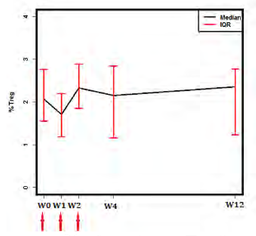
r-hIL-7 led to a substantial increase of CD4$^+$ T cell count without preferential increase of the proportion of T reg cells



CD4$^+$ T cell dynamics after first (N=95) and second (N=49) complete cycles



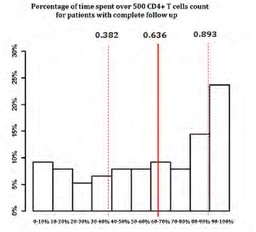
CD4$^+$ T cell dynamics after a first complete cycle and according to the number of CYT107 injections received



% of regulatory T cells (CD4$^+$FoxP3$^+$) after the first cycle up to week 12 for INSPIRE 2 patients (N=23)

Time spent above 500 CD4$^+$ cells/μL

The median time spent above 500 cells/μL for patients with a follow up of at least 21 months (N=76) was 13.7 (8.4, 20.1). That is half of these patients spent more than 63 % of their follow up with more than 500 CD4$^+$ T cells/μL.



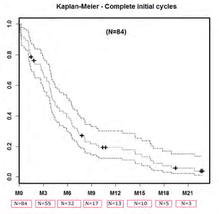
Factors associated with dropping below 550 cells/μL

After adjustment for the baseline CD4$^+$ T cell count, there was no significant difference of the effect of the maintenance cycles compared to the initial cycle whereas receiving incomplete cycles with only one injection increased the probability to fall below 550 CD4$^+$ cells/μL

Shared gamma frailty model (R package Frailtypack)

Factor	HR	95% CI	P-value
$\geq$ 200 CD4$^+$/μL	1		
$\leq$ 200 CD4$^+$/μL	11.101	(4.019, 30.661)	< 0.001
Initial cycle	1		
Mainten. cycle	0.862	(0.510, 1.455)	0.569
3 injections	1		
2 injections	2.270	(0.787, 6.554)	0.023
1 injection	4.289	(1.323, 13.902)	

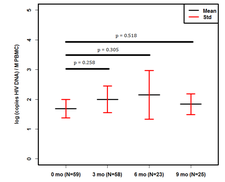
Frailty parameter: θ:0.822 (P-value: 0.006)



Viral dynamics

An increase frequency of viral blips was observed in patients treated by r-hIL-7 without substantial impact on the HIV DNA dynamics

Period	Total measures	RNA>200 cp/ml % of measures	RNA>200 cp/ml % of patients
Before IL-7 started	419	0.5	1.8
Once IL-7 started (from D0 to D28)	1738 (805)	2.1 (0.8)	15.9 (7.1)

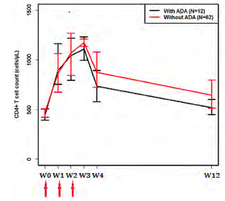


log (copies of HIV DNA by million of PBMC) in CYT107 arm INSPIRE 3 patients

Percentage of patients presenting binding (ADA) and neutralizing (NADA) anti-CYT107 antibodies

Binding and neutralizing antibodies were generated mainly after the second cycle without substantial impact on the CD4$^+$ T cell response to further injections

	1st cycle INSPIRE 2	1st cycle INSPIRE 3	2nd cycle INSPIRE 2	2nd cycle INSPIRE 3
ADA	26 % (6)	16 % (14)	87 % (20)	82 % (72)
NADA	-	1 % (1)	38 % (9)	39 % (34)



Median and IQR of CD4+ T cells within second cycle according to the presence of ADA after the first cycle

Adverse events (AE) - Related Adverse Events (RAE)

From the total of RAEs, most of them were grade $\leq$ 1 (77.6%), grade 2 (20.7%) and 1.7% grade $\geq$ 3. Five (5) patients presented an anaphylactic/allergic reaction, and symptoms were resolute with antihistaminic and corticosteroids.
Ten (10) patients presented AE grade $\geq$ 3 hypophosphataemia, of which 3 possible RAE. An AST/ALT elevation of grade 4 was reported in 1 patient as a probable RAE.

Conclusions

Repeated cycles of r-hIL-7 was safe and led to a substantial increase of the time spent above 500 cells/μL. The clinical benefit of such strategy needs to be evaluated in phase III clinical trial.

Acknowledgements

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