Immunotherapy in HIV disease: recent developments and future directions

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Use of highly active antiretroviral therapy (HAART) has changed the natural history of HIV infection decreasing mortality and morbidity [1]. Clinical improvement is due to qualitative and quantitative immune reconstitution after control of viral replication. Despite use of HAART, we are not able to fully reconstitute immune competence [2]. The goal of immunotherapy strategies (cytokines, therapeutic vaccines or immunomodulators), is to accelerate or improve the immune restoration and/or control of viral replication in association with cART or after its interruption. At the state of knowledge, it is clear that the decline of CD4 is only partially explained by the level of viral load; host factors and the degree of immune activation, play an essential role in the immunodeficiency. On the other hand, the level of immune restoration achieved with cART reduces AIDS events, but is not enough to obtain of mortality and morbidity rate close to the general population, except for patients with prolonged high CD4 T levels (> 500/mm3).

Adjuvant immunotherapy with cytokines has been proposed as the ideal approach to modulate immune response by directly targeting the immune system.

Intermittent treatment with Interleukin-2 (IL-2).

Since 1995 several studies have been conducted to investigate IL-2 in HIV-infected individuals immunological non-responders [3-9]: IL-2 administration for 2-5 days every 6-8 weeks is safe and induces reconstitution of the CD4+ compartment, with no significant interference with HIV viral replication. IL-2 increases CD4+ cells [10].

In our centre, to evaluate the safety and efficacy of 3 regimens of intermittent subcutaneous IL-2, 61 patients were randomly assigned to ART plus IL-2 (three different arms with different dosage) or ART alone. Low doses (3 million IU twice a day every 4 weeks) of IL-2 induced a stable increase of peripheral CD4 cells, both naïve and memory.

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Figure 1. Superior effect of interleukin-2 plus antiretroviral therapy (ART) vs ART alone on increasing absolute circulating T cells in ESPRIT trial.

Figure 1 shows a comparison of CD4+ cell counts between patients treated with ART alone and those treated with ART plus IL-2. The graph illustrates the time spent in the categories of CD4+ cell count: less than 300 cells/mm³ and greater than 600 cells/mm³. The data indicates that patients in the ART + IL-2 group had a higher CD4+ cell count compared to the ART control group with a significant difference (p < 0.001). The table below summarizes the number of patients (No. Pts) in each category over different years (Years).
Group (ACTG) received a single dose of CYT 99 007, the non glycosylated form of IL-7. The trial was randomized against a placebo and stratified according to viral load at entry. In the first stratum (undetectable viral load at entry), 17 patients were enrolled in 4 cohorts corresponding to dose levels between 3 and 60 μg/dose of CYT 99 007; 13 patients received CYT 99 007. In stratum 2 (50 to 50,000 copies/mL of HIV RNA at entry), 8 patients were enrolled in 2 cohorts, corresponding to 2 dose levels (3 and 10 μg/kg); 6 patients received CYT 99 007. Dose escalation has stopped in both strata and preliminary unblinded results are available for stratum 1: maximum tolerated dose was 30μg/Kg; at this dose level, most common AEs were transient LFT elevation and local reactions. Single-dose rhIL-7 induced T-cell proliferation, down-regulation of IL-7Ra, and transient T-cell increases. The maximum
tolerated dose was 30 µg/kg. Biologic activity at all tested doses suggests a favourable therapeutic index of this cytokine for potential use in HIV infection [16].

Phase I/II multicentric study evaluated the safety and biological effects of escalating doses of recombinant human IL-7 (CYT 99-007) in HIV-infected patients with CD4 between 100 and 400 cells/mm³ and viral load below 50 copies/ml [17]. They received 8 subcutaneous injections 3 times/week. Median CD4 counts increased of 95% at day 21 and remained significantly above baseline at week 12 (p<0.01); CD4 increase was dependent on the dose (3 and 10 mcg / kg) and it was durable for up to 48 weeks after cessation of IL-7. The possible effect of IL-7 on viral replication is being investigated in phase I / II under way, with a glycosylated form of IL-7 administered once a week subcutaneously. Glycosilated form of IL-7 have these expected advantages: it shows less or no immunogenicity in primates and its pharmacokinetic and pharmacodynamic profile may allow for a greater interval between doses. Our centre is involved in this Phase I/IIa randomized placebo controlled, single-blind multicenter dose-escalation study of subcutaneous intermittent Interleukin-7 (CYT107) in chronically HIV-infected patients with CD4+ cells count between 101-400/mm³ and plasma HIV-RNA<50 copies/ml after at least 12 months of HAART. The primary objective of the study is to determine the safety and identify a biologically active dose of CYT107. Future studies are necessary to understand clinical benefits of CD4+ rise.

**CCR5 antagonists**

The therapeutic armamentarium against HIV has recently gained Maraviroc belonging to a novel class of antiretrovirals, the CCR5 antagonists. In MOTIVATE 1 and 2 [18, 19] studies Maraviroc, as compared with placebo, resulted in significantly greater suppression of HIV-RNA at 48 weeks in previously treated patients with R5 HIV-1 who received optimized background therapy. Interestingly, the change from baseline in CD4 counts was also greater with maraviroc (p<0.001). These results are confirmed at 96 weeks [20]. A metanalysis of different drug combinations showed that CCR5 antagonists increase CD4 count better than other drugs. This new class, with new mechanism of action, could be considered an immunomodulator. In fact these are first drugs with virological action but also with direct action on immune system. Our published data suggest that some antiretroviral combinations containing maraviroc could rise CD4 significantly [21, 22]; CD4 increase is better with association with one or two active drugs [18, 19].

**Discussion**

IL-2 represented the most promising immunomodulant approach of HIV-infection treatment. Several studies confirmed qualitative and quantitative immune reconstitution of adjunct IL-2 versus HAART alone. Unfortunately, results of Phase III clinical trials SILCAAT and ESPRIT, with extensive follow up (median years of follow up 7.7) underline
that this immunological advantage does not translate into clinical benefits; in some cases immune reconstitution should be a disadvantage, with major risk of inflammatory-based events. Results of these trials change the scenario of immunotherapy in HIV disease: Phase I results of IL-7 trials are encouraging, but in terms of CD4+ rise too, not in terms of clinical outcome. Could immunotherapy have another chance after these results?

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