

Long-Term Benefit of Cyclosporin A Coupled with Highly Active Antiretroviral Therapy in Primary HIV-1 Infection

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INTRODUCTION

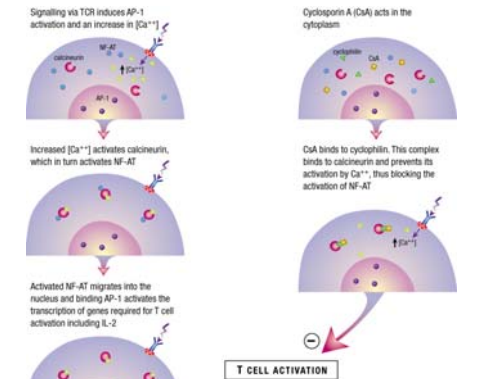
Massive immune activation is a major feature of primary HIV-1 infection, and is a chief mechanism of HIV-1 infection-associated disease. The hypothesis to couple cyclosporin A (CsA) with HAART during primary HIV-1 infection (PHI) to decrease immune activation has been successfully tested in a pilot study (Rizzardini et al., *J Clin Invest* 2002;110:881-886), suggesting that reducing immune activation may be beneficial for immunologic measures.

The rationale of the study, i.e., to rapidly shut down immune activation, particularly during primary infection, is supported by a series of observations: (a) primary HIV infection is characterized by a heightened state of cellular activation; (b) initiation of HAART is accompanied by an increase in the relative proportion of CD4⁺ T cells that proliferate and/or are activated; (c) massive productive HIV-1 infection and virus spreading require proliferating and/or activated target cells; and (d) massive immune activation may lead to exhaustion and rapid elimination of HIV-specific CD8⁺ and CD4⁺ T cells.

STUDY DESIGN

In an open-label prospective, controlled trial carried out at the Centre Hospitalier Universitaire Vaudois in Lausanne, Switzerland, and the San Raffaele Scientific Institute in Milan, Italy, 77 adults with confirmed diagnosis of primary HIV-1 infection have been consecutively treated with PI-containing HAART, either alone (n = 43, control group) or coupled with CsA (n = 34, CsA group). All patients started therapy within 72 hours of screening. HAART contained 2 NRTI along with either 2 PI or 1 RTV-boosted PI, equally distributed between treatment groups. CsA was administered throughout the first 8 weeks of therapy, at a dose achieving CsA blood levels stably >100 ng/mL. After 8 weeks, CsA was discontinued and HAART was continued alone. Immunologic and virologic measures were compared over 120 weeks in the 2 groups, both with a median follow-up of 28 months (range 3 to 36). Plasma viral load was measured with Amplicor assay (LOD 50 copies/mL). The primary measures of therapy (CsA + HAART and HAART only) effects were changes in plasma HIV-1 RNA and peripheral blood CD4⁺ T cell counts over time. Changes in CD4⁺ T cell count and percentage observed in the CsA cohort were compared with those observed in the control cohort. The HIV-1 RNA values underwent log₁₀ transformation before analysis. The proportion of enrolled subjects who had HIV-1 RNA levels lower than 50 copies/mL was calculated over time (on treatment analysis). Within-subject value changes were compared using the paired Student's t test. Results were analyzed by the χ^2 test in the case of dichotomous data and by the Student's t test in the case of continuous variables. The level of association between dependent and independent variables has been tested with regression analysis. All P values were two-tailed, and a P value of less than 0.05 was considered to indicate statistical significance. The mechanism of action of CsA is briefly described in Figure 1. CsA inhibits T cell activation by interfering with calcineurin and thus IL-2 synthesis and release, in a reversible manner. CsA activity is lymphocyte-specific and blocks quiescent lymphocytes in phase G₀-G₁, thus reducing the number of cells that can be activated and support new rounds of HIV-1 infection.

Figure 1: The Mechanisms of Inhibition of T Cell Activation by Cyclosporin A



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RESULTS and DISCUSSION

Baseline characteristics were comparable in the two treatment groups (Figure 2). All patients developed signs and symptoms of primary HIV-1 infection. Overall, adherence to HAART was good in both treatment groups, and CsA was very well tolerated in all patients. None of the patients developed opportunistic infections.

Figure 2: Baseline Characteristics

Patients with PHI ¹ (N=77)	Treatment Group		P-value
	CsA+HAART (N=34)	HAART only (N=43)	
Age (years)	38.2±9.7	34.3±8.9	0.73
Gender (% Females)	21	24	NS ²
Risk (% MSM/IVDU/HETERO) ³	47/9/44	39/3/58	NS
CD4 ⁺ T Cell Counts (cells/ μ l)	480±197	461±262	0.73
CD4 ⁺ T Cell Percentage (%)	19.8±9.5	21.6±11.3	0.46
CD4/CDB Ratio	0.40±0.4	0.48±0.5	0.46
HIV-1 RNA levels (log ₁₀ copies/ml)	5.86±0.15	5.64±0.14	0.33

Continuous variables are expressed as mean±SD (standard deviation)

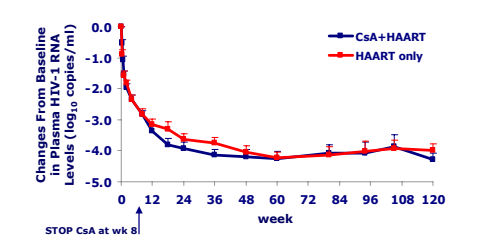
¹PHI denotes primary HIV-1 infection

²NS denotes not significant

³MSM denotes men who have sex with men, IVDU i.v. drug-users, and hetero heterosexuals

Initiation of therapy induced effective and sustained suppression of HIV-1 RNA replication in both groups over time (Figure 3). No significant differences from baseline in the levels of virus replication were observed throughout the 120 weeks of follow-up. However, it is worth noting that, at week 36, the proportion of patients attaining plasma HIV-1 RNA levels below 50 copies/mL was significantly higher in patients receiving CsA along with HAART than in patients receiving HAART alone (96 vs 70%, respectively, P=0.011).

Figure 3: Mean Changes From Baseline in Plasma HIV-1 RNA Levels in Patients Receiving Either CsA + HAART or HAART Only



During the first 56 days of CsA therapy, the net increase over baseline values in both CD4⁺ T cell percentage and cell counts was significantly greater in patients receiving CsA in combination with HAART than in those receiving HAART alone (Figures 4 and 5). The increase in CD4⁺ T cells was paralleled by a decrease in CD8⁺ T cell percentage and count (data not shown), inducing a more rapid normalization of the CD4/CDB ratio in patients receiving CsA + HAART than in those taking HAART alone: 1.09 vs 0.78 (p = 0.02) at the week 2, 1.14 vs 0.79 (p = 0.005) at week 4, and 1.25 vs 0.69 (p = 0.001) at week 8 (Figure 6).

It is worth noting that levels of plasma HIV-1 RNA measured at baseline significantly predicted changes from baseline in CD4⁺ T cell counts after 2 weeks of therapy ($\beta=0.45$, 95% CI 28-328, P=0.022, regression analysis), indicating that, in patients receiving CsA in addition to HAART, higher levels of plasma HIV-1 RNA at baseline are associated with greater increases in CD4⁺ T cell counts after 2 weeks of therapy (Figure 7).

Figure 4: Mean Changes From Baseline in CD4⁺ T Cell Counts in Patients Receiving Either CsA + HAART or HAART Only

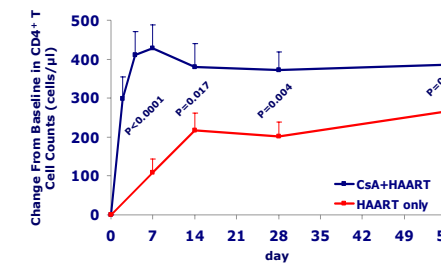


Figure 5: Mean Changes From Baseline in CD4⁺ T Cell Percentage Levels in Patients Receiving Either CsA + HAART or HAART Only

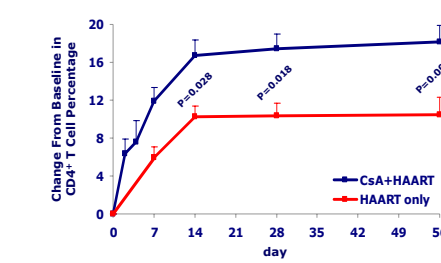


Figure 6: Mean Changes From Baseline in CD4/CDB Ratio in Patients Receiving Either CsA + HAART or HAART Only

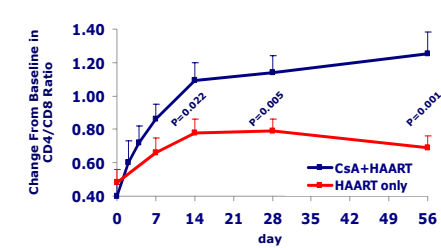
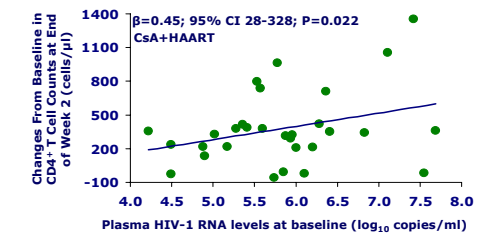


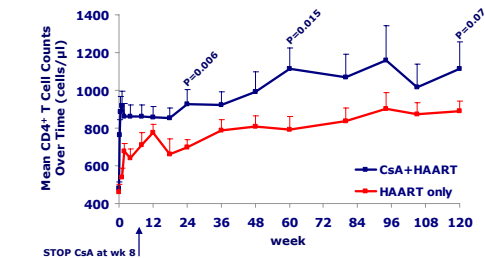
Figure 7: Baseline Plasma HIV-1 RNA Levels Predict Changes From Baseline in CD4⁺ T Cell Counts at Week 2



The most striking effect of the addition of CsA to HAART in patients with primary infection was observed on CD4⁺ T cell responses, inducing a very rapid (within 1 week) restoration of CD4⁺ T cells, both in terms of percentage and absolute numbers. Furthermore, the early increase in CD4⁺ T cell counts following treatment with CsA + HAART was predicted by the levels of HIV-1 RNA measured in plasma at baseline (Figure 7). Greater levels of plasma HIV-1 RNA might reflect an earlier diagnosis of primary infection as well as a state of increased cellular activation that is selectively targeted by the administration of CsA. Overall, these results provide support for the hypothesis that, during primary HIV-1 infection, CsA in combination with HAART might drastically decrease the heightened state of cellular activation. This, in turn, may reduce the number of activated CD4⁺ T cells that support massive virus production, and may prevent sequestration of CD4⁺ T cells into lymphoid tissue, i.e., the site of antigen presentation and productive HIV-1 infection. Indeed, the greatest benefit in terms of CD4⁺ T cell numbers was achieved after only 7 days of treatment with CsA, suggesting that CsA probably interferes with the efficacy of the infectious process by reducing the exit of CD4⁺ T cell death induced by apoptosis, incoherent bystander mechanisms, direct virus cytopathicity, or some combination of these during the very early phases of infection.

During long-term follow-up (Figure 8), it is worth noting that the beneficial effect of CsA therapy on CD4⁺ T cells continued after CsA treatment was stopped, since the net gain in CD4⁺ T cells remained significantly greater in patients who had taken CsA + HAART than in those who had taken HAART alone.

Figure 8: Mean±SEM CD4⁺ T Cell Counts Over 120 Weeks of Follow-Up in Patients Receiving Either CsA + HAART or HAART Only



CONCLUSIONS

- Decreasing immune activation in the very early phases of HIV-1 infection has a beneficial impact on the long-term course of the disease, contributing to the establishment, following primary HIV-1 infection, of a more favourable immunologic set-point that affects the ultimate pattern and rate of disease progression
- The benefits achieved with HAART during primary HIV-1 infection may be extended via the use of an immune-modulating strategy interfering with early pathogenic events

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