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Structured Antiretroviral Therapy Interruption as a form of Immune-based Therapy in HIV-1 Infection

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Abstract

Recently, a huge interest on structured therapy interruption (STI) has emerged in the HIV field. STI is based on the concept of boosting HIV-1 specific immune responses with a kind of autologous vaccination by cycling antiretroviral drug interruptions in subjects who respond to antiretroviral therapy. Since the concept of HIV-1 eradication is no longer tenable, the enhancement of HIV-1 specific immune responses in order to keep viremia at low levels for prolonged periods has become an urgent treatment goal. However, there is no current effective therapeutic vaccine to boost HIV specific immune responses. Efforts to stop treatment have failed so far. Rapid rebound of plasma viral load has been reported after variable periods of successful HAART in subjects with acute or chronic HIV-1 infection. On the other hand, sporadic reports have identified subjects who were able to control virus replication after discontinuation of HAART initiated during primary infection. Fifteen abstracts from the Seventh Retrovirus Conference held in San Francisco in February 2000 described data from STI in different HIV-infected populations. All these studies try to answer the question about the possibility of inducing an HIV-1 specific immune response during primary HIV infection (PHI) or chronic HIV infection (CHI), and whether STI may be effective as an immune-based therapy. Data accumulated suggest that it might be possible to induce specific helper and CTL responses in HIV-1 infection, both in PHI and CHI. The responses obtained during PHI seem to be stronger, and the helper responses were maintained during the periods on HAART, which are of benefit for increasing and maintain CTL responses during the periods off therapy. The responses obtained during CHI are weaker, but do exist. The main problem is that both CTL and helper responses diminished during the periods on therapy. However, these findings may open a new approach for the treatment of CHI. If the immune system is able to learn how to fight effectively against HIV-1 infection it might be possible to develop therapeutic vaccines in order to improve the control of HIV-1 infection obtained during HAART.

Key words

Structured treatment interruption (STI). CTL. HAART. Viral load.

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Introduction

A huge interest in structured therapy interruption (STI) has emerged during the past year. Many pilot studies have been reported in several meetings. Frequently, however, there is a misunderstanding between the concepts of 'drug holidays' and STI. The concept of drug holidays is based on preliminary studies by Veronica Miller *et al.*[1] and introduces the hypothesis of discontinuation of antiretroviral therapy in failing patients with multi-resistant virus in order to permit the fitter wild type virus to replace the resistant mutant strains. This topic is not the object of the present review. On the other hand, STI is based on the concept of boosting HIV-1 specific immune responses with a kind of autologous vaccination by cycling antiretroviral drug interruptions in patients who respond to antiretroviral therapy. This structured therapeutic intervention is now one of the most intensively studied areas in HIV clinical research.

HIV eradication

The identification of long-lived, latently infected CD4+ T cells[2,3] and the data recently reported by Finzi *et al.*,[4] indicating that the mean half-life of this reservoir was 44 months, prolonged the estimation for the eradication of HIV-1 infection from the previously calculated 1-3 years of successful highly active antiretroviral therapy (HAART)[5-7] up to 10-60 years[4]. Ramratnam *et al.*[8] explained this wide range showing that replication competent HIV-1 in resting cells decay with a t1/2 of 6 months, but only in individuals with plasma HIV-1 RNA consistently below 50 copies/mL. Slower decay would occur in individuals with intermittent blebs of viremia probably due to replenishment of the pool. In addition, others[9,10,11] reported that, despite apparently successful treatment with HAART during several years, residual HIV-1 replication persists. As a strategy to accelerate the elimination of this pool, Chun *et al*[12] associated an intermittent adminitration of IL-2 with continuous HAART. They demonstrated that this approach might lead to a substantial reduction in the pool of resting CD4+ T cells that contain replication-competent HIV. In fact, virus could not be isolated from the peripheral blood CD4+ T cells in three patients receiving IL-2 plus HAART, despite the fact that large numbers of resting CD4+ T cells were cultured[12]. However, viral load rebounded rapidly even in these 3 patients after discontinuation of therapy[13]. Taken together, these data would imply that the concept of HIV-1 eradication is no longer tenable. Augmentation of HIV-1 specific immune responses to help maintain viremia at low levels for prolonged periods has become an urgent treatment goal. However, there is no current effective therapeutic vaccine to boost HIV specific immune responses.

HIV-specific immunity and control of HIV-1 infection

HAART has reduced the incidence of AIDS-defining diseases by 85%[14]. However, it implies indefinite treatment with at least three drugs, and therefore inconvenience, side effects, and high cost. Efforts to stop treatment have failed so far. Rapid rebound of plasma viral load has been reported after variable periods of successful HAART in subjects with acute or chronic HIV-Yinfection who discontinue therapy[15-19]. Whether viral load rebound starts from hidden reservoirs in latently infected lymphocytes or from ongoing replication is currently being actively investigated[2,13,20]. This rebound could be due to the lack of specific immune response against HIV-1 antigens in patients treated with HAART alone[21]. In addition, both CD4+ T cells and CTL response decline after 6 months of effective HAART[22,23].

There are increasing data supporting the effectiveness of specific CD4+ T cells and CTL response against HIV-1 antigens[23-29]. The more compelling data come from recent studies with SIV-infected rhesus macaques that support the notion that CD8 T cells, by a mechanism not yet elucidated, are required for controlling HIV replication. With this model, the *in vivo* depletion of CD8 cells by monoclonal antibodies was temporally associated with significantly higher levels of viral replication[24,26-27]. With the recovery of CD8 cells, the SIV levels diminished[24,27].

Furthermore, stronger immune responses correlate with a less aggressive disease course. Although in most patients HIV eventually destroys the immune system, the rare long term non-progressors (LTNP) tolerate HIV infection for many years without apparent ill effects. Their CD4 counts remain in the normal range and their plasma viral load is very low or undetectable. Most LTNPs show a strong and persistent cytotoxict lymphocyte (CTL) response towards HIV[25,30,31,33,34]. Such a response is transient in patients who are not LTNPs, allowing continued proliferation of HIV resulting in immunosuppression[35].

The above mentioned data present three fundamental questions to be answered in the next few years. The first question is: Which immune functions are critical for the control of HIV replication? The second question is: It is possible to induce immune responses during primary or chronic infections? Thirdly: Which immune-based therapies elicit better recovery of an effective T-cell function?

Inducing effective specific immune responses against HIV-1 antigens

Is it possible to induce persistent CTLs and CD4+ specific helper responses in patients who would otherwise progress to immunodeficiency? Would such patients be able to contain viral replication after interruption of HAART? Preliminary data are available and indicate that this may be possible.

Patients treated very early in HIV infection (during primary infection or shortly thereafter) develop a powerful, persisting CTL and CD4+ proliferative response directed against HIV[25,36]. Two of such patients had poor adherence to their drug regimens, and discontinued therapy with a rebound of plas-

ma viremia but resumed drug therapy for variable periods, and finally ceased therapy. In both, HIV-RNA fell to below detection for 21 and 14 months off all antiretroviral therapy. Both had broad and strong HIV-1 specific CTL responses that were boosted at the time of first drug discontinuation, which was associated with viral rebound. When therapy ended, broad and strong CTL responses were measured and have remained high[37]. Another patient treated with ddI, hydroxyurea and indinavir stopped treatment and had a relapse of viremia. He was again treated, his plasma viral load dropped, and he stopped treatment again. This patient did not relapse after more than one year off treatment. He has a powerful CTL against HIV[38]. Three patients with stable viremia were treated with HAART containing hydroxyurea using the following schema: 3 weeks therapy, 1 week treatment interruption, then two cycles of 3 months therapy followed by treatment interruption and re-initiation as soon as rebound (> 5,000 copies/mL) occurred. Viremia became undetectable (< 400 copies/mL) after each initiation of therapy. Rebound-free intervals were extended from 7 days during the first interruption to 37 days during the third treatment interruption[39]. Finally, rhesus macaques infected with SIV/Mac251 (baseline viremia 200000, 500000 and 1.1 million copies/mL) were treated with hydroxyurea, didanosine and the nucleotide analog PMPA, using an intermittent schedule (two cycles of 3 weeks therapy followed by treatment interruption). SIV was allowed to rebound until it reached more than 5,000 copies/mL. Although viral rebound occurred, it was controlled in all three animals, and was followed by a reduced steady-state level of virus in the absence of therapy. This level was < 5,000 for 6 weeks during the first interruption, and it decreased to < 200 for at least 10 weeks after the third interruption. Two monkeys are now without relapse after 4 and 6 months, respectively[39].

These isolated cases of patients who were able to control virus replication after discontinuation of HAART initiated during primary infection[37,38,40,41] suggest that HIV-1 specific immune responses could be restored in patients who started HAART at this early stage of HIV-1 disease, and that this response precludes the viral rebound[25,37]. However, these responses are very similar to those of long-term non-progressors[25,31-34] and it is not possible to exclude the fact that the control of the infection and the immunologic responses could have occurred independently of antiretroviral therapy.

Structured therapy interruption (STI)

The occasional data of cyclic treatment interrup-tion leading to control of HIV-1 infection instigated many researchers to investigate this therapeutic approach. Fifteen abstracts from the Seventh Retrovirus Conference held in San Francisco in February 2000 described data from STI in various HIV-infected populations. Overall, these studies try to answer the question about the possibility of inducing HIV-1 specific immune responses during PHI or CHI, and if STI may be effective as an immune-based therapy.

STI in patients starting HAART during primary HIV infection

Three of these abstracts reported data during primary HIV infection (PHI). Altfield *et al.*[42] reported on seven acutely infected individuals who were identified before seroconversion and immediately treated with HAART. After over one year of HAART, individuals underwent STI. Low magnitude CTL responses against 1-4 epitopes were seen before STI. After interruption of therapy, virus rebounded within 1-8 weeks [levels not given] and HAART was reintroduced. CTL responses were boosted in all STI patients, who gained a median of two new recognised epitopes (range 0-3) and increased their responses to previously recognised epitopes. Zala *et al.*[43] followed 8 patients treated during PHI with d4T, ddI and nevirapine with (n = 5) or without HU (n = 3). After 48 weeks of treatment, patients were offered an STI with re-challenge allowed after 30 days if viral rebound was confirmed. All 8 rebounded to > 5,000 copies after 21 days. HU did not significantly affect the kinetics of rebound. All patients responded to re-challenge (viral load <500) within a median of 4 weeks. Jin *et al.*[44] treated 4 individuals with AZT/3TC/indinavir within 100 days (median 60) after acute infection. After 2.5 years of therapy, subjects were vaccinated with ALVAC1452/rgp160. One week after their final vaccination, these 4 patients chose to stop therapy. In two individuals (50%) delayed viral rebound was observed; HIV-RNA became detectable at 68 and 85 days post vaccination. The other two patients (50%) experienced rapid viral rebound with detectable virus within 13 and 23 days. Delayed rebounders had significant increases in CTLs to more than one viral antigen following vaccination. The rapid rebounders either had a monospecific response to *gag* or no measurable CTL response to vaccination. After 4 to 8 months off therapy, the delayed rebounders had RNA levels of 3.75 and 2.52 logs, while the rapid rebounders had 3.55 and > 4.70 logs after 4 months off therapy.

The weakness of these studies is that they are not randomised, they do not offer clear data about the effectiveness in control viral replication (i.e. viral load set-point reached) and they report only short periods of follow-up with a few interruptions of therapy. On the other hand, these data strongly support the hypothesis that, given the recovery of helper response in patients treated during PHI[25] and the loss of CTL response after 6 months of HAART[23], STI could intensify and maintain the specific HIV-1 CTL response, since the specific helper response is strong due to the early initiation of therapy.

STI in patients starting HAART during chronic HIV infection

Of the 12 abstracts presented about STI in CHI, 3 focused on pathogenetic findings but not on the

clinical effectiveness of this approach. Chun *et al.*[20] suggested that the viral responsibility of rebounds observed upon treatment cessation may not come exclusively from the pool of latently infected, resting CD4+ cells harbouring replication-competent HIV. They used quantitative microculture and heteroduplex mobility assays to compare viral RNA from reservoirs and plasma before and after rebound in nine patients who underwent STI. HIV-RNA was identical in only two out of nine patients and divergent in seven. Sherer *et al.*[45] identified retrospectively 13 HIV-infected individuals who achieved a viral load below 500 copies/mL a minimum of 90 days after stopping antiretroviral therapy (median 2.5 years, range 3 months - 5.6 years). Pre-therapy viral loads (available for 7/13 patients) were very low (< 500-9,000 copies/mL). They concluded that isolated cases of individuals with low or undetectable HIV RNA upon stopping therapy is not always evidence of an exceptional therapeutic effect. Orenstein *et al.*[46] reported that after discontinuation of HAART lymph node tissue viral rebound parallels plasma viral load rebound.

Nine abstracts focused on the effectiveness of STI in CHI. Three of the only reported data after the first discontinuation of therapy. Hatano *et al.*[47] treated 12 patients with HAART and did not observe differences in viral load set-point after the first interruption of therapy. However Smith *et al.*[48] did find a lower viral load set-point after the first interruption in 9 patients treated with IL-2 plus HAART. Kilby *et al.*[49] studied the viral load rebound in 5 patients after 8 days off therapy and found that in 3 of them viral load did not rebound. Six abstracts reported data on more than 1 interruption of therapy. Two concluded that longer follow-up is needed to observe a clear response to STI[50,51], one report did not observe any response after STI[52] and three found a good virological and specific helper and CTL anti-HIV-1 response after STI[53-55]. Fagard *et al.*[50] presented the Swiss-Spanish Intermittent Treatment Trial (SSITT). Eligible patients were antiretroviral naive before HAART, did not experience treatment failure during HAART, maintained viral load < 50 for at least 6 months, and were NNRTI naive. Treatment was stopped for two weeks and resumed for eight weeks, in four cycles. Data of 57 out of a projected 120 patients enrolled between April-September 1999 were reported. Pre-HAART median CD4 count was 398 and viral load 4.56 logs. At that time 16 patients had already experienced 2 STIs and 4 had 3 STIs. Viral rebound in the first STI occurred in 28/43 (65%) and during the second STI in 12/16 (75%). The two rebounds were similar in amplitude ($p = 0.2$). After 7 weeks of re-treatment, 3/20 evaluable and compliant patients did not achieve viral load < 50 (RNA = 62, 105 and 147). This is the first study addressing the effectiveness of STI with sufficient number of patients. On the other hand, these are very preliminary data, informing basically about the possibility of performing a multicentre-multinational study on STI, and about the safety of this approach. The knowledge of the viral load set-point reached after the last interruption of therapy will be decisive to address the question about the efficacy of STI in CHI. Ruiz *et al.*[51] assessed virologic and immunologic changes during an STI in 25 chronically-infected individuals who achieved long-lasting (> 2 years) viral suppression and a CD4/CD8 ratio of >1. They were randomised to stay on HAART (group 1, N = 13) or interrupted for a maximum of 30 days or until the viral load increased over 3000 (group 2, N = 12), then resuming the same prior HAART. Two out of 12 patients did not rebound after 30 days during the first STI; only 1 maintained viral load < 20 during the second STI. Among the rest, viral load became detectable (>20) for a median of 14 and 15 days during the first and second STIs. Viral load rose exponentially with a mean half-life of 1.6 and 2.2 days during the first and second STIs. They found: i) STIs were not associated with CD4 reductions or clinical complications after two years of effective viral suppression; ii) virus rebounded in most, but not all patients; iii) virus was effectively controlled upon re-challenge; and iv) that 'HIV-specific helper T-cell responses may require subsequent cycles of STI to keep viral replication under control'.

The study by Carcelain *et al.*[51,52] reports no immunologic benefit due to treatment interruption. They assessed HIV-specific T cell responses and HIV control after repeated (3 or 4) 7-21 day treatment interruptions in three individuals whose viral load had stayed < 20 copies/mL and whose CD4 count rose to > 400 for at least two years on HAART. Before treatment interruption, there were no significant CD4 and weak CD8 responses to HIV. In patient 1, three 7-day interruptions did not induce viral rebound or T helper stimulation. In patient 2, Th-1 responses increased only at the first rebound. In patient 3, Th1 responses occurred at each interruption but were transient. HIV-specific CD8 cell frequencies did not increase. Interferon gamma producing CD4 cells were observed after the TI, but the cells were rapidly deleted after virus replication resumed. His study is similar to that of Kilby *et al.*[49] where there were brief STI. It is possible that a viral load rebound to higher levels should be beebed or for longer duration to induce more durable HIV-specific responses.

The reports by Lori *et al.*[53], Papasavvas *et al.*[54] and our group[55] coincide in the possibility of inducing an effective immunologic response against HIV-1 in CHI. Lori *et al.*[53] conducted a case-control study comparing nine individuals receiving ddI and hydroxyurea (HU) in the PANDA cohort with eight individuals on HAART. They conclude that, unlike HAART patients, PANDA patients have low but detectable viremia and vigorous HIV-specific cellular immune responses. PANDAs and matched HAART controls interrupted therapy for eight weeks. Failure during STI was defined as a viral load rise to over 10,000 copies or CD4 drop to below 200. Five of the eight HAART patients failed by week six and had to restart therapy, whereas no PANDA had to restart during eight weeks of follow-up. Papsavvas *et al.*[54] from the Wistar Institute in Philadelphia measured anti-HIV cellular (CD4 and CD8) immune responses

in five chronically infected individuals who had maintained viral suppression on HAART and subsequently went on STI and compared them with five untreated controls. During the STI, the five previously suppressed individuals were able to significantly increase broad antiviral T-helper and IFN-gamma secreting CD8 T-cell responses as a result of complete treatment interruption. There were substantially fewer changes in the control group. The STI group experienced significant increases in anti-HIV T-helper responses against p24 and gp160 preceding significant increases in IFN-gamma secreting CD8 T-cell responses against viral envelope antigens. After a median 46 days of STI, three subjects restarted HAART and achieved 99% reductions in plasma viremia by 21 days and maintained or further increased the cell-mediated anti-HIV responses. The remaining two subjects stayed off therapy, maintained high cell-mediated responses, and maintained RNA below 1,080 copies. These observations suggest that CD4 and CD8-mediated cellular immune responses against autologous HIV-1 are augmented as a result of temporary treatment interruption in a subset of chronically infected individuals. We reported on 10 chronically infected patients given three consecutive STI cycles after 52 weeks of d4T, 3TC and ritonavir or indinavir and whose viral load had been < 20 copies for > 32 weeks[55]. Three cycles of STI were administered separated by 6 months of the same triple HAART combination. Viral rebound occurred in all cases with a mean doubling time of 2.23, 3.38 and 3.25 days. At the 2nd STI, in 4/9 patients viral load rebounded to levels similar to baseline and then dropped spontaneously by 0.8, 1.3 and 2.09 logs respectively. After the third STI, the viral load setpoint appeared significantly lower than baseline in 4 out of 7 patients. These 4 patients developed strong and broad CTL responses and a strong CD4+ lymphocyte proliferative response to HIV-1 antigens during the interruption of therapy, but they lost it when they resumed therapy. Drug resistance mutations were not detected after any of the STIs. Therefore, STI may induce effective specific cytotoxic and CD4+ lymphocyte proliferative immune responses against HIV-1 antigens associated with a spontaneous drop in plasma viral load in chronic HIV infection.

Conclusions

It is possible to induce specific helper and CTL responses in HIV-1 infection, both in PHI and CHI. The responses obtained during PHI seem to be stronger, and the helper responses were maintained during the periods on HAART, which are of benefit for increasing and maintain CTL responses during the periods off therapy. The responses obtained during CHI are weaker, but do exist. The main problem is that both CTL and helper responses diminished during the periods on therapy. However, these findings may open a new approach to treatment of CHI. If the immune system is able to learn how to fight effectively against HIV-1 infection it might be possible to develop therapeutic vaccines in order to improve the control of HIV-1 infection obtained during HAART. The last unanswered question is how long STI could be effective in the control of HIV-1 infection. The current periods of follow-up are too short, but ongoing studies should provide the right answer within the next few months.

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