ELSEVIER

Journal of Clinical Virology 31S (2004) S48–S54

JOURNAL OF CLINICAL VIROLOGY

www.elsevier.com/locate/jcv

T-cell vaccination against anti-CD4 autoimmunity in HIV-1 infected patients☆

Rivka Abulafia-Lapid[a,*], Zvi Bentwich[b], Yael Keren-Zur[a], Irun R. Cohen[c], Henri Atlan[a,d]

[a] *The Human Biology Research Center (HBRC), Hadassah University Hospital, Ein-Kerem, Jerusalem 91120, Israel*
[b] *Neve Or AIDS Center, Kaplan Medical Center, Hebrew University-Hadassah Medical School, Rehovot, Israel*
[c] *Department of Immunology, The Weizmann Institute of Science, Rehovot, Israel*
[d] *Faculte de Medecine Broussais-Hotel Dieu-EHESS, 54 Blvd Raspail, 75006-Paris, France*

Abstract

Background: Highly active antiretroviral therapy (HAART) is frequently associated with only partial restoration of CD4 T-cell levels. Autoimmunity to CD4 T-cells may account for the persistence of the CD4 T-cell lymphopenia in such cases.
Objective: To document T-cell autoimmunity to CD4 in HIV-infected patients and to determine if T-cell vaccination against CD4 autoimmunity is feasible and safe.
Study design: Seven out of 20 HIV-infected patients undergoing HAART who manifested T- cell reactivity to rCD4, gp120 and to recall antigens (Tetanus toxoid and Candida) were treated with T-cell vaccines composed of glutaraldehyde treated autologous, activated T-cells, and enriched in anti CD4-reactive T-cells. The response of the seven vaccinated patients was compared to seven non-vaccinated HIV-1 infected subjects.
Results: Five out of seven responded with a decrease in anti-CD4 autoimmunity, associated with a persistent increase in their CD4 T-cell levels; just one of the control patients showed increased CD4 levels. No change in HIV plasma viral loads and no adverse effects were detected in any of the T-cell vaccinated patients.
Conclusions: The persistence of CD4 T-cell lymphopenia despite effective anti-retroviral treatment may be associated with anti-CD4 autoimmunity. T-cell vaccination with autologous autoimmune CD8 T-cells may decrease such autoimmunity and increase CD4 T-cell numbers.
© 2004 Elsevier B.V. All rights reserved.

Keywords: CD4; T-cell vaccination; HAART; HIV-1; AIDS; Autoimmunity

1. Introduction

The hallmark of HIV-1 infection is a continuous attrition of CD4 T-cells, leading progressively to immune deficiency (Levy, 1993; Pantaleo and Fauci, 1995). The CD4 molecule is a co-receptor for HIV (Dimitrov et al., 2001) and the gp120 molecule of the HIV envelope serves as the viral ligand for CD4 (Gabriel and Mitchell, 1996). Productive HIV infection is cytopathic for T-cells in vitro (Lifson et al., 1986; Casella and Finkel, 1997), but only a fraction of CD4 T-cells are actually infected with HIV (Anderson et al., 1998). Therefore, it is unclear whether HIV infection of CD4 T-cells may, by itself, account for the magnitude of the CD4 T-cell loss in HIV-infected persons (Anderson et al., 1998; Ho et al., 1995). It is possible that other indirect effects of HIV on the host immune system may participate in the CD4 decline. The persistence in several patients of CD4 T-cell leukopenia, despite a reduction in the viral load by highly active antiretroviral ther-

Abbreviations: HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; FCS, fetal calf serum; PHA, phytohemaglutinine; APC, antigen presenting cell

☆ The work was supported by grants from the Ishaia Horowitz Foundation, and the Institute for Advanced Therapy, NY, USA.

* Corresponding author. Tel.: +972 2 677 6521; fax: +972 2 642 1203.
E-mail addresses: rivka_abulafia@yahoo.com (R. Abulafia-Lapid), atlan@ehess.fr (H. Atlan).

1386-6532/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.jcv.2004.09.017

apy (HAART) (Fleury and Pantaleo, 1999), indeed supports this notion, as we have previously suggested (Grossman et al., 1993; Leng et al., 2001). Although indirect mechanisms such as thymic attrition (Douek et al., 1998) may account for the CD4 T-cell decline by preventing CD4 T-cell renewal, a degree of CD4 leukopenia might also result from the killing of CD4 T-cells, both HIV-infected and non-infected, by cytotoxic CD8 T-cells (Israel-Biet et al., 1990; Zarling et al., 1992; Hoffenbach et al., 1989; Grant et al., 1994; Zinkernagel and Hengartner, 1994). HIV infection may trigger an autoimmune T-cell response to the CD4 molecule (Morrow et al., 1991; Salemi et al., 1995; Caporossi et al., 1998; Lanzavecchia, 1995) that could lead to the destruction of uninfected CD4 T-cells.

T-cell vaccination is a procedure in which attenuated or killed autoimmune T-cells are used as vaccines to activate immune regulation of an autoimmune disease (Cohen, 1986). T-cell vaccination has been studied in experimental animals (Ben-Nun et al., 1981; Cohen, 2000; Lider et al., 1988), and lately has been used clinically to induce the down-regulation of human autoimmune diseases such as multiple sclerosis (Zhang et al., 1993; Cohen, 2002; Zhang et al., 1995, 2000). Atlan and colleagues have previously suggested that autologous anti-CD4 T-cells might be used as vaccines to down-regulate anti-CD4 autoimmunity in HIV-infected patients (Atlan et al., 1993, 1994; Atlan and Cohen, 1996).

The present study was primarily designed to investigate T-cell autoimmunity to CD4 in HIV-infected patients. Our positive findings then led us to initiate an open trial of T-cell vaccination in which we vaccinated seven of the patients with their own anti-CD4 T-cells, and followed them up for close to 2 years. Seven control-infected subjects were also followed up to monitor spontaneous changes in CD4 T-cell levels.

2. Methods

2.1. Subjects

We recruited 20 HIV-infected patients (median age 40 years) (CDC Group II/III) from the Kaplan Hospital AIDS Center (Rehovot, Israel) (Table 1). Their CD4 T-cell numbers ranged from 93 to 575 cells/μl (median 357.5) and their plasma viral loads (Amplicor, Hoffman-LaRoche, Basel, Switzerland) from <400 to 37,000 copies/ml (median 9390) (Table 1). The study was approved by the Ethical Committees of the Hadassah University Hospital, Ein-Kerem, Jerusalem, and the Kaplan Medical Center, Rehovot, Israel. Before entering the study, all patients signed an informed consent. All patients except one were receiving HAART; patient P18 had refused this treatment. Blood was also obtained from 20 HIV-seronegative, healthy donors, through the Tel-Hashomer Central Blood Bank, to serve as controls (data not shown). In addition, seven (CP1–CP7) HIV-infected patients, three males and four females, receiving HAART (median 4 years) were used as historical controls during at least 4 years of observation. Their CD4 T-cell numbers ranged from 108 to 224 cells/μl (median 190, 17%) and their plasma viral loads from <400 to 8300 (median 3.890).

Table 1
Clinical features of HIV-1 infected patients

Patients	Age/sex	Time from diagnosis (years)	Duration of HAART (years)	HIV plasma VL[a] (copies/ml)	CD4 cells		rCD4
					(Cell/μl)	(%)	
P1	63/M	11	2.3	<400	348	(21)	4.2
P2	35/M	9	2	14000	394	(28)	4.5
P3	36/M	10	2.3	1500	327	(26)	7.0
P4	55/M	5	1.8	<400	289	(29)	2.0
P5	41/M	2	3.2	2000	172	(17)	2.0
P6	50/M	12	0.5	37000	247	(14)	5.7
P7	40/M	13	2	<400	388	(23)	7.8
P8	33/F	5	1.2	<400	549	(37)	1.3
P9	33/F	10	4	13600	93	(6)	5.8
P10	27/M	7	1	<400	452	Nd	3.0
P11	34/M	9	4.3	5290	390	(20)	2.6
P12	37/M	4	3	<400	657	(37)	3.4
P13	42/M	1.5	1.4	<400	512	(34)	1.0
P14	42/M	8	3	<400	634	Nd	1.7
P15	41/M	16	2.2	11300	376	(7)	6.0
P16	53/M	2.6	2.5	<400	379	(24)	5.1
P17	41/M	7	4	<400	333	(17)	1.0
P18	30/M	0.3	Untreated	11600	338	(24)	2.1
P19	40/F	5	4	<400	269	(26)	5.2
P20	34/M	8	4	7480	232	(21)	2.0
Median	40	7.5	2.3	9390	357.5	(22.5)	$3.7 \pm 2.1^{\#\#}$

<400: Below detection, Nd: not determined.
[a] Viral load.
$P < 0.0001$.

2.2. T-cell proliferation assay

Peripheral blood mononuclear cells (PBMC) were isolated by density centrifugation on Ficoll Paque (Pharmacia Biotech, Uppsala, Sweden) from 30 to 40 ml of heparinized venous blood, obtained from patients or from the blood bank (see above). Cells were cultured in RPMI 1640 medium (Biological Industries Ltd., Beit Haemek, Israel), supplemented with 10% fetal calf serum (FCS) (Gibco BRL, Buffalo, NY, USA), 1% sodium-pyruvate, 1% L-glutamine, 1% penicillin/streptomycin (10,000 U/ml/10,000 mg/ml) (Seromed, Berlin, Germany) and 2% Hepes (1 M, pH7.3) (Biological Industries, Beit Haemek, Israel). Specific cell proliferation was assayed by ^{3}H-thymidine incorporation, as described previously (Abulafia-Lapid et al., 1999). The antigens used were soluble recombinant human CD4 and HIV-1 gp120 proteins (2–5 μg/ml each) expressed in baculovirus (Intracell Corp., Cambridge, MA, USA), tetanus toxoid (Connaught Lab. Inc., PA, USA) and candida (Hollister-Stier, Toronto, Canada) (data not shown, but discussed). Statistical analysis was performed using the InStat 2.01 computer program, and *P*-values using the Mann–Whitney non-parametric test.

2.3. Protocol for the preparation of the T-cells used for T-cell vaccination (TCV)

rCD4-reactive T-cells were generated from 30 to 40 ml of blood obtained from each patient for vaccine preparation

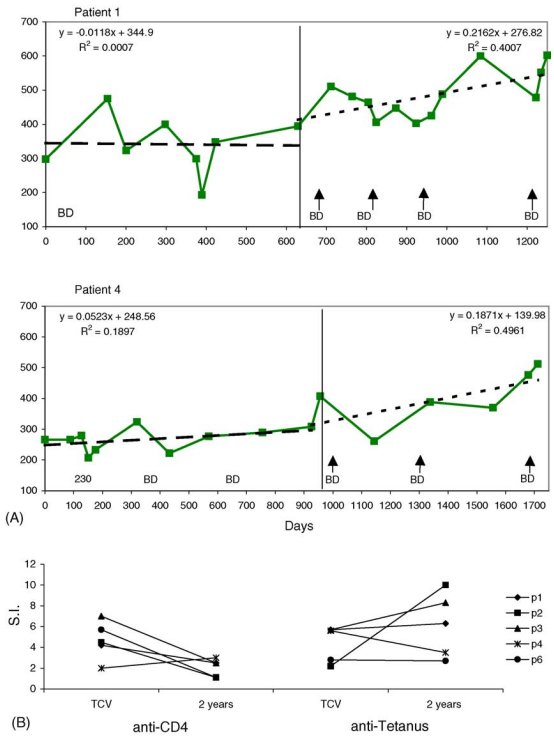

Fig. 1. (A) CD4 T-cell numbers following TCV in two patients. We measured the absolute numbers of peripheral blood CD4 T-cells during the 2 years both before (– – – –) and after (- - -) the initiation of TCV. The vertical line represents the time points of the initial TCV. The arrows represent the time points of the TCV injections. We calculated linear regression slopes of CD4 T-cell numbers for each of the patients, before and after TCV. The plasma viral loads are indicated under the slopes by numbers (copies/ml blood); BD indicates below detection. (B) T-cell proliferative responses to rCD4 and to tetanus toxoid following TCV. We measured T-cell proliferative responses before and 2 years after the onset of TCV by ^{3}H-thymidine incorporation assay. The results are presented as the S.I. Patients: P1 (♦), P2 (■), P3 (▲), P4 (*), and P6 (●).

(Zhang and Raus, 1995). All cultures were performed according to the procedures required for the preparation of biological products to be used in humans. Briefly, PBMC were isolated from the blood of each of the patients, cultured with 3 μg/ml phytohemaglutinine (PHA) (Murex Diagnostic Ltd., UK), and expanded with 5–20 U/ml recombinant interleukin-2 (rIL-2) (Boehringer Mannheim GmbH Mannheim, Germany) for 11 days. The cultures were re-stimulated on day 14, with irradiated rCD4-pulsed antigen presenting cells (APCs), according to Zhang et al. (1993), and were further grown for another 7 days. On day 21, the cells were inactivated for 5 min at room temperature with 1.0% glutaraldehyde (Sigma, St Louis, MO, USA) and prepared for injection. Aliquots of 10×10^6 CD4 reactive-T-cells were frozen in liquid nitrogen, to be used later for second and third booster vaccinations, at 2–6 month intervals (Fig. 1A).

2.4. TCV and patient follow-up

Trained medical personnel administered vaccinations (Kaplan Hospital, Rehovot, Israel) in an AIDS clinic to seven HIV-infected patients: P1–P7 in Table 1 (CD4 T-cell numbers 172–394; 327 median; viral load <400–37,000; median 2000; median duration of disease 10 years). The effects of the TCV were evaluated on the basis of clinical, immunological, and virological assessments, before, during and following the first injection for 1–2 years. Seven HIV-infected patients under HAART (three males and four females; median age 53; disease duration 9.5 years) were not vaccinated and were followed as controls for the changes in of CD4 counts in the absence of TCV. The clinical follow-up of the patients consisted of a complete physical examination, and blood tests including a complete blood count and biochemistry (liver function and renal function). Following each injection, the patients remained at the clinic for 2 h to watch for any immediate side-effects, and remained under close surveillance by the treating physician for an additional 7 days to record any adverse events. Adverse effects were monitored following the World Health Organization (WHO) protocol, looking for local signs at the site of injection and general systemic symptoms, such as fever, rash, and anaphylaxis. The immunological follow-up consisted of: (a) total lymphocytes and T-cell subset counts (CD3, CD4 and CD8) at the indicated time points, and (b) specific proliferative responses of PBMC to rCD4, gp120 and recall antigens (tetanus and candida), before and 1–2 years after vaccination. The virological follow-up consisted of an assessment of HIV plasma viral load, 2 weeks after the first injection and thereafter approximately every 3 months.

2.5. Flowcytometry

Percentages of CD4 and CD8 T-cells were assessed by flow cytometry analysis using FACSCalibur and monoclonal antibodies specific for CD3, CD4 and CD8 from Becton–Dickinson immuno-cytometry Systems, San Jose, CA.

3. Results

3.1. Patients

Table 1 summarizes the clinical features of the 20 HIV-infected patients. Their median age was 40 years, seventeen were male and three were female, and the duration of their infection from time of diagnosis, ranged from 4 months to 13 years (median, 7.5 years). All but one of the patients was treated with HAART, and the duration of treatment varied (median, 2.3 years). In 10 of the patients, plasma viral levels were below detection (<400 copies per ml), and in the other ten, plasma viral loads ranged from 1500 to 37,000 copies per ml. Most of the patients had various degree of CD4 T-cell leukopenia (median, 357 CD4 T-cells per μl blood).

3.2. Anti-CD4 autoimmunity

We screened 20 HIV infected patients and 20 healthy blood donors. These patients were tested for T-cell proliferation assays to recombinant human CD4 (rCD4), to recombinant gp120 (rgp120), to tetanus toxoid, and to Candida and showed only responses to rCD4. Seven patients were selected for receiving TCV. The response to CD4 was significantly higher in the HIV group (mean S.I. 3.7 ± 2.1), compared to the controls (mean S.I. 1.4 ± 0.35; $P = 0.0001$) (data not shown). If one considers the mean $\pm$ 2 S.D. of the S.I. from the controls (2.1) as the upper limit of normal, 12 of the 20 HIV-infected patients (60%) had S.I. values that were higher than this value (from 2.6 to 7.8). Thus, the HIV patients showed a significantly enhanced T-cell response to CD4.

3.3. T-cell vaccination

An open pilot study of T-cell vaccination against CD4 autoimmunity was carried out in seven of the HIV patients (P1–P7), all of whom were receiving HAART (Table 1). The cells used for vaccines were derived from peripheral blood mononuclear cells, stimulated and expanded for 21 days (see Section 2). The CD4-reactive T-cells were enriched in CD8 T-cells, relative to the starting population (Table 2) and manifested high IFN-γ and low IL-10 expression, therefore representing an enriched T1 type population. Prior to the vaccination, the cells were fixed with 1.0% glutaraldehyde so as to kill them and inactivate any live viruses they could be harboring. In addition, no HIV particles were found in the supernatants of these cultures (Amplicor, Hoffman–LaRoche, Basel, Switzerland). It is noteworthy that no virus was detectable after 21 days of in vitro culture in the T-cells of patients with viral loads in the blood; patients P2, P3, P5 had plasma viral loads of 14,000, 1500 and 2000 copies/μl respectively, and 5%, 11%, and 19% of CD4 T-cells, respectively, remained in the T-cell vaccine preparation. P6, despite having only 7% remaining CD4 T-cells

Table 2
Vaccine T-cells are enriched $CD8^+$ cells

Patient	Fresh PBMC		T-cell vaccine			
	CD4 (%)	CD8 (%)	CD4(%)	CD8 (%)	IFN-γ (pg/ml)	IL10 (pg/ml)
P1	28	27	15	53	3090	34
P2	19	52	5	92	2560	82
P3	26	56	11	73	1390	78
P4	30	43	27	61	1760	170
P5	16	39	19	70	5530	38
P6	14	40	7	88	1240	110
P7	23	55	9	86	Nd	*Nd*

in the T-cell vaccine preparation, had a plasma viral load of 37,000 copies/μl Tables 2 and 3). Nevertheless, the T-cell cultures used for vaccination were free of virus even before fixation.

The autologous T-cell vaccine preparations were injected subcutaneously with about 10^7 T-cells in 1 ml of saline administered three or four times at intervals of 2–6 months. No clinical or laboratory side effects were observed during the 1 year (P5 and P7) or 2 years (P1, P2, P3, P4, P6) follow-up period. Five of the seven vaccinated subjects responded with an increase in the levels of circulating CD4 T-cells, compared to the mean levels of CD4 T-cells observed during the 2-year-period preceding the T-cell vaccination (Table 3A). Furthermore, as can be seen in Table 3B, a spontaneous rise of CD4 levels was not observed in the control group of HIV infected patients that also received HAART and had a similar degree of HIV suppression during the same period of time. Interestingly, despite an adequate response to HAART (HIV below detection), two of the patients, P1 and P4, had shown no consistent increase in CD4 T-cells during the period of 1.8–2.5 years that preceded their vaccination (Fig. 1A). In both patients, T-cell vaccination initiated a consistent increase in the numbers of CD4 T-cells over a 2-year-period, while HIV plasma levels remained below detection.

In addition, no increase in the plasma viral loads were detected after 1 year in patients P5 and P7, and after 2 years in patients P1, P3, P4 and P6 following TCV. In fact, P5 and P6 manifested a significant decrease, from 2000 copies/μl to below detection and from 37,000 to 5600 copies/μl, respectively (Table 3A). Patient P2 is the only exception. However, his viral load was unusually unstable from the beginning, with ups and downs which continued after TCV. In addition, his CD4 cell count improved significantly during the 2 years following TCV.

In five of the seven patients (P1, P2, P3, P4 and P6), we were able to test the T-cell responses to rCD4 2 years after vaccination. A fall in the anti-CD4 response was observed in four patients, and a rise in the T-cell response to tetanus toxoid was seen in two of them (Fig. 1B). Two patients (P5 and P7) have been followed for only 1 year and therefore were not included in this figure. Taken together, T-cell vaccination using autologous T-cells as a vaccine, was associated with a decrease in anti-CD4 autoimmunity and a concomitant increase in CD4 T-cell numbers, in certain subjects.

Table 3
Peripheral blood CD4 T-cell numbers and viral load after T-cell vaccination

Patient number	CD4 cells/μl blood			HIV plasma viral load (copies/ml)	
	Pre-vaccination[a]	Post-vaccination[b]	Change[c] (%)	Pre-vaccination[a]	Post-vaccination[b]
A. TCV treated HIV-1 patients					
P1	353 ± 100	600	70	<400	<400
P2	413 ± 112	701	69	14000	229000
P3	290 ± 52	523	80	1500	1490
P4	275 ± 41	512	86	<400	<400
P5	187 ± 54	277	48	2000	<400
P6	252 ± 106	385	52	37000	5690
P7	237 ± 96	450	89	<400	<400
B. Untreated HIV-1 subjects					
CP1	142 ± 29	167	18	5130	958
CP2	202 ± 43	256	27	6930	6890
CP3	136 ± 33	220	61	<400	<400
CP4	190 ± 52	224	18	3790	<400
CP5	198 ± 40	279	40	<400	<400
CP6	153 ± 41	235	53	3890	1220
CP7	226 ± 90	230	2	8300	5830

[a] Mean of 2 years before vaccination.
[b] Measured after 1 year in patients P5 and P7 and after 2 years in the others.
[c] Mann–Whitney non-parametric Student *t*-test; $P = 0.0070$.

4. Discussion

Here, we describe an initial trial of T-cell vaccination. Seven of the 20 HIV infected patients that were selected and screened for TCV manifested T-cell reactivity to the CD4 molecule. Their autoreactivity to CD4 appears to be independent of the plasma HIV viral load because no correlation was found between the viremia (Table 1) and the in vitro T-cell proliferative response to CD4 (correlation coefficient = 0.2817).

Although the study was not blinded and lacked a placebo control group, it generated some results worthy of comment. First, T-cell vaccination in HIV-infected patients is feasible; it was indeed possible to raise a sufficient number of autologous T-cells to fashion a vaccine, even in persons with detectable viremia. Secondly, the resulting vaccines were composed of T-cells enriched for CD8 cells that produced more IFN-γ than IL-10, suggesting that they were T1 type of cells (Table 2). Thirdly, some of the subjects appeared to respond to the vaccination by a reduction in anti-CD4 autoimmunity (Fig. 1B) and by a rise in absolute numbers of peripheral blood CD4 T-cells. All but one of the patients (P5) showed an above 50% change (median 70%; Table 3 and Fig. 1A); this was not seen in a comparable group of non-vaccinated patients followed for the same period of time; only two patients (CP3 and CP6) showed a change above 50% (median 27%; $P = 0.007$; Table 3). Fourthly, in no instance did we see any aggravation of the patient's condition, in particular any decrease in CD4 cell numbers. In one patient (P2), the viral load was highly unstable before and after TCV, but a significant increase in CD4 cell counts from 400 to 700 cells/microliter of blood was observed 2 years after TCV (Table 3A).

Finally, as mentioned above, some patients entered the study with relatively high viral loads, and the T-cell preparations used as vaccines still contained appreciable numbers of CD4 cells. Nevertheless, no virus could be detected in the supernatants of the cell cultures. This suggests that some of the T-cells in the culture may have had anti-HIV activity in vitro. However, it is unlikely that the vaccination produced any undesirable immune response against HIV-specific CTLs, since there was no significant clinical deterioration following vaccination. With the exception of patient P2 discussed above, none of the patients showed an increase in viral load after TCV. Actually, two vaccinated subjects showed a significant decrease in their viral load 2 years after TCV, indicating, at least, that TCV did not decrease the efficacy of the ongoing antiviral therapy. It remains to be determined whether the HIV-infected CD4 cells were killed in culture by CTL specific for HIV antigens or by anti-CD4 autoimmune CTL. How HIV infection may activate autoimmunity to CD4 is unknown, but conceivably, it could be related to an immunogenic alteration of the CD4 molecule following the binding of gp120 to CD4 (Morrow et al., 1991; Salemi et al., 1995; Caporossi et al., 1998; Lanzavecchia, 1995), and/or to the abnormal state of activation of the immune system in HIV-infected persons (Leng et al., 2001; Salemi et al., 1995).

It is conceivable that the increase of CD4 following TCV was not related to the vaccination itself, but was rather the long-term, albeit delayed, outcome of HAART. However, our observations in a group of un-vaccinated patients suggest that the TCV might indeed be responsible for the increase. The existence of patients that have a discordant response to HAART, suppression of HIV plasma viral load without an increase in their CD4 numbers, is well established. The seven un-vaccinated patients serving as a control group are an example of this phenomenon. The increase in CD4 T-cell counts in the TCV treated subjects and the lack of toxicity are encouraging.

In conclusion, our study shows that TCV against the autoimmunity anti-CD4 cells in HIV-infected patients is feasible and safe with no adverse effects. However because of the small number of test subjects, our study does not allow us to draw firm conclusions regarding its therapeutic efficacy. The efficacy of TCV needs to be tested in a phase II clinical trial that we hope will be undertaken in the near future.

Acknowledgments

H. Atlan is the incumbent of the S. Mark Taper Chair of Biophysics and the Director of the Human Biology Research Center. Z. Bentwich is now Executive Vice President for Medicine and Research, Rosetta Genomics Inc., Ein Kerem, Israel. I.R. Cohen is the incumbent of the Mauerberger Chair of Immunology, and the Director of the Center for the Study of Emerging Diseases. We thank Joelle Nataf, M.D. (Hotel Dieu Hopital, Paris, France) for useful comments and technical assistance; the late Ziva Weissman, Ph.D., Ilana Eliezer and Dov Barak, R.N. (Kaplan Medical Center, Rehovot, Israel) for their clinical assistance. We are particularly grateful to Jean Claude Ameisen, M.D. (INSERM, CHU Bichat, Paris, France) for his critical and thorough review of the manuscript.

References

Abulafia-Lapid R, Elias D, Raz I, Keren-Zur Y, Atlan H, Cohen IR. T-cell proliferative responses of type 1 diabetes patients and healthy individuals to human hsp60 and it peptides. J Autoimmun 1999;12:121–9.

Anderson RW, Ascher MS, Sheppard HW. Direct HIV cytopathicity cannot account for CD4 decline in AIDS in the presence of homeostasis: a worst-case dynamic analysis. J AIDS 1998;17:245–52.

Atlan H, Cohen IR. T-cell vaccination for HIV-seropositive patients. In: Gupta S, editor. Immunology of HIV infection. New York: Plenum Press; 1996.

Atlan H, Gersten MJ, Salk PL, Salk J. Can AIDS be prevented by T-cell vaccination? Immunol Today 1993;14(5):200–2.

Atlan H, Gersten MJ, Salk PL, Salk J. Mechanisms of autoimmunity and AIDS: prospects for therapeutic intervention. Res Immunol 1994;145:165–83.

Ben-Nun A, Wekerle H, Cohen IR. Vaccination against autoimmune encephalomyelities with T-lymphocytes cell lines reactive against myelin basic protein. Nature 1981;292:60–1.

Caporossi AP, Bruno G, Salemi S, Mastroianni C, Falciano M, Salotti A, et al. Autoimmune T-cell response to the CD4 molecule in HIV-infected patients. Virol Immunol 1998;11(1):9–17.

Casella CR, Finkel TH. Mechanisms of lymphocyte killing by HIV. Curr Opin Hematol 1997;4:24–31.
Cohen IR. Regulation of autoimmune disease, physiological and therapeutic. Immunol Rev 1986;94:5–21.
Cohen IR. Tending adam's garden. In: Evolving the cognitive immune self. San Diego: Academic Press; 2000.
Cohen IR. T-cell vaccination for autoimmune disease: a panorama. Vaccine 2002;20:706–10.
Dimitrov AS, Xiao X, Dimitrov DS, Blumenthal R. Early intermediates in HIV-1 envelope glycoprotein-mediated fusion triggered by CD4 and co-receptor complexes. J Biol Chem 2001;276(32):30335–41.
Douek DC, McFarlnd RD, Keiser PH, Gage EA, Massey JM, Haynes BF, et al. Changes in thymic function with age and during the treatment of HIV infection. Nature 1998;396:90–695.
Fleury S, Pantaleo G. T-cell regeneration in HIV-infected subjects under highly active antiretroviral therapy. Int J Mol Med 1999;4(1):91–7.
Gabriel JL, Mitchell WM. Functional design of potential inhibitors of human immunodeficiency virus (HIV) binding to CD4+ targeT-cells: a molecular model of gp120 predicts ligand binding. Drug Des Discov 1996;14(2):103–14.
Grant MD, Smail FM, Rosenthal KL. Cytotoxic T-lymphocytes are associated with CD4+ lymphocyte depletion in HIV-1 infection. J AIDS 1994;7:571–9.
Grossman Z, Bentwich Z, Herberman RB. From HIV infection to AIDS: are the manifestations of effective immune resistance misinterpreted? Clin Immunol Immunopathol 1993;69:1–13.
Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature 1995;373:123–6.
Hoffenbach A, Langlade-Demoyen P, Dadaglio G, Vilmer E, Michel F, Mayaud C, et al. Unusually high frequencies of HIV-specific cytotoxic T lymphocytes in humans. J Immunol 1989;142:452–62.
Israel-Biet D, Venet A, Beldjord K, Andrieu JM, Even P. Autoreactive cytotoxicity in IV-infected individuals. Clin Exp Immunol 1990;81:18–24.
Lanzavecchia A. How can cryptic epitopes trigger autoimmunity? J Exp Med 1995;181:1945–8.
Leng Q, Borkow G, Weisman Z, Stein M, Kalinkovich A, Bentwich Z. Immune activation correlates better than HIV plasma viral load with CD4 T-cell decline during HIV infection. J AIDS 2001;27:389–97.
Levy J. Pathogenesis of human immunodeficiency virus infection. Microbiol Rev 1993;75:183–289.
Lider O, Reshef T, Beraud E, Ben-Nun A, Cohen IR. Anti-idiotypic network induced by T-cell vaccination against experimental autoimmune encephalomyelitis. Science 1988;239:181–3.
Lifson JD, Reyes GR, McGrath MS, Stein BS, Engleman EG. AIDS retrovirus induced cytopathology: gian T-cell formation and involvement of CD4 antigen. Science 1986;232:1123–6.
Morrow WJ, Isenberg DA, Sobol RE, Stricker RB, Kieber-Emmons T. AIDS virus infection and autoimmunity: A perspective of the clinical, immunological, and molecular origins of the autoallergic pathologies associated with HIV disease. Clin Immunol Immunopathol 1991;58:163–80.
Pantaleo G, Fauci AS. New concepts in the immunopathogenesis of HIV infection. Annu Rev Immunol 1995;13:487–512.
Salemi S, Caporossi AP, Boffa L, Longobardi MG, Barnaba V. HIV gp120 activates autoreactive CD4-specific T-cell responses by unveiling of hidden CD4 peptides during processing. J Exp Med 1995;181:2253–7.
Zarling JM, Ledbetter JA, Sias J, Fultz P, Eichberg J, Gjerset G, et al. HIV-infected humans but not chimpanzees have circulating cytotoxic T lymphocytes that lyse uninfected CD4+ cells. J Immunol 1992;144:2992–8.
Zhang J, Hong J, Rivera VM, Killian J, Zhang JZ. Preferential recognition of TCR hypervariable regions by human anti-idiotypic T-cells induced by T-cell vaccination. J Immunol 2000;164(8):4011–7.
Zhang J, Medaer R, Stinissen P, Hafler D, Raus J. MHC-restricted depletion of human myelin basic protein-reactive T-cells by T-cell vaccination. Science 1993;262:1451–4.
Zhang JW, Raus JCM, editors. T-cell vaccination and autoimmune disease, New York Landes Co.;1995.
Zinkernagel RM, Hengartner H. T-cell-mediated immunopathology versus direct cytolysis by virus: implications for HIV and AIDS. Immunol Today 1994;15:262–8.