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Korean Red Ginseng Significantly Slows CD4 T Cell Depletion over 10 Years in HIV-1 Infected Patients: Association with HLA

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Abstract : We have shown that long-term intake of Korean red ginseng (KRG) delays disease progression in HIV-1 infected patients. In the present study to investigate whether this slow progression was associated with protective human leukocyte antigen (HLA) alleles as well as with KRG-intake, we have performed clinical analysis of 31 HIV-1 infected patients who have been living for more than 10 years without any antiretroviral therapy. Average amount of KRG-intake over 130 ± 16 months was 4,797 ± 4,921 g and the annual decrease in CD4 T cell (AD) was 30 ± 29/μL. We observed significant correlations among amount of KRG-intake, AD ($r = -0.53$, $P < 0.01$), and plasma HIV-1 RNA copy ($r = -0.35$, $P < 0.05$), along with a significant correlation between KRG-intake and HLA score ($r = 0.49$, $P < 0.01$), whereas there was no significant correlation between HLA score and AD or viral load. When the 31 patients were divided into 2 groups based on the amount of KRG-intake, the AD (14/μL) in the 16 patients who had taken higher amounts of KRG was significantly less than that (49/μL) in the 15 patients with a little or no KRG-intake ($P < 0.01$). These data indicate that KRG-intake significantly slows CD4 T cell depletion in HIV-1 infected patients.

Key words : Korean red ginseng, HLA, HIV-1 RNA, CD4 T cells, Correlation

INTRODUCTION

The introduction of highly active antiretroviral drug therapy (HAART) has proven effective in the treatment of human immunodeficiency virus (HIV)-1 infected patients.[1,2] HAART alone, however, cannot eradicate the virus in the human body because of the long-lasting reservoirs of the DNA provirus and mutations generating drug-resistant strains.[3-5] Because production of Th1 cytokines is gradually reduced in HIV-1 infected patients,[6-7] the immune modulator interleukin (IL)-2 has recently been combined with HAART. Although this therapy significantly increases the number of circulating CD4 T cells, it has many limitations, including frequent and severe adverse effects, making its continuous application problematic. Thus, a new modality is required for more effective therapy of AIDS.

Ginseng is the root of the perennial herbs of *Panax ginseng*, which contains a series of tetracyclic triterpenoid saponins (ginsenosides) and many trace elements, including selenium, manganese, copper, and cobalt. In the Orient, *Panax ginseng* C. A. Meyer has been used as a drug for more than 2000 years.[8] At present, ginseng is one of 12 medicinal herbs commonly used in America,[9] as well as the most well-known and valued herb in Korea, China, and Japan. Ginseng is considered an adaptogenic agent, which enhances physical performance, promotes vitality and increases resistance to stress and ageing, and possesses immunomodulatory activity.[10-12]

Regarding its immunomodulatory properties, a double-blind, placebo-controlled study in normal human volunteers revealed that ginseng significantly increases neutrophil function, CD4 T cells and NK cell function.[11] Ginseng was also found to increase the cellular immune functions of peripheral blood mononuclear cells (PBMC) from AIDS patients and normal individuals.[12] Recently an acidic polysaccharide from ginseng was shown to induce Th1 cell and macrophage cytokines,[13] and this immunostimulating

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effect was blocked in the presence of antibodies to IL-2 and interferon (IFN)-γ.[14] In addition, treatment of chronic *Pseudomonas aeruginosa* pneumonia in rats with ginseng was found to reduce bacterial load and lung pathology, as well as to increase IgG2a in serum, suggesting that the antimicrobial properties of ginseng are due to its induction of Th1-like responses. In addition, xylanase[15] and panaxgin from ginseng have been reported to possess inhibitory effects against HIV-1 reverse transcriptase.

We had an opportunity to try Korean red ginseng (KRG) for HIV-1 infected patients for 6 months beginning in late 1991. Surprisingly, we observed that the intake of 5.4 g KRG per day had various beneficial effects, including increases in the CD4 and CD8 T cell counts, and body weight, and decrease in soluble CD8 antigen (sCD8) in serum.[16] We also observed significant inverse correlations between the duration of KRG-intake and the mutation rate of HIV-1 *in vivo*, and between the duration of KRG-intake and the progression rate in HIV-1 infected patients.[17] Data analysis over 60 months revealed that KRG treatment more significantly delayed the decrease in CD4 T cells than ZDV monotherapy as well as slowing the development of resistance to antiretroviral drugs.[18,19] Among the patients involved in the first KRG trial, some have maintained their CD4 T cell counts for more than 10 years without antiretroviral drug therapy.

Although the prognosis of HIV-1 infected patients has been found to be strongly associated with genetic backgrounds of HLA genotypes,[20-24] HLA haplotypes have never been determined in Korean HIV-1 infected patients, suggesting the possibility that the effects of KRG may be HLA-dependent. In the present study, we evaluated the effects of KRG-intake and HLA class I and transporter associated with antigen-processing (TAP) 2 in 31 HIV-1 infected patients who lived more than 10 years after diagnosis without antiretroviral therapy. Our data show that KRG-intake significantly slowed CD4 T cell depletion and maintained lower levels of HIV RNA copy and sCD8. Protective HLA haplotypes alone did not show significant correlations in slowing CD4 T cell depletion and HIV RNA copy. However, consistent KRG-intake and protective HLA types together significantly improved the clinical parameters including frequencies of requirement for HAART treatment and hospital admissions.

MATERIALS AND METHODS

Study population

Of the 268 HIV-1 infected patients from 1985 until April 1993, we selected all patients who have lived more than 10 years after their initial HIV-1 diagnosis without antiretroviral therapy and whose CD4 T cell counts were available throughout that period. Our study population thus consisted of 31 patients (Table 1).

Treatment with KRG

Since November 1991, we have studied with KRG treatment in HIV-1 infected patients. The daily dose of KRG was 5.4 grams (g). We instructed patients to take 6 capsules (300 mg per capsule) orally three times per day. KRG was supplied to a total of about 150 patients although the amount of KRG supplied and the mode of therapy varied according to the time at which each patient was included in the study. Among the 31 patients in this study, 25 had been treated with KRG and 6 had not. Over the 130 ± 16 months study period, the mean amount of KRG supplied per patient was 4,797± 4,921 g (range; 0-19,302 g) at the recommended dose of 5.4 g/day[16,17]. Of the 25 patients treated with KRG, 6 took only the KRG we supplied, 13 had also purchased additional KRG, and 6 showed poor adherence (Table 2). Informed written consent was obtained from all study participants or their guardians.

Laboratory procedures

DNA was isolated from PBMC[18] and HLA-A, -B, and -C typing was performed using the amplification-refractory mutation system (ARMS)-PCR method.[25-27] Each tube contained a primer mix consisting of the allele- or group-specific primer pairs, as well as a positive control primer matching the nonallelic sequences. There were 32 sets specific for HLA-A, 27 sets for HLA-B, and 23 sets for HLA-C. PCR reactions were performed in a volume of 13μL modified from the class I ARMS-PCR reference manual of the 12th International Histocompatibility Workshop. The PCR products were on electrophoresis of 1.5% agarose gels prestained with ethidium bromide. Variants in TAP were identified by SSCP.[28]

Assigning prognostic scores to HLA alleles or allele combinations

An HLA scoring profile was developed by means of a detailed analysis using Cox proportional hazard models to compute the relative hazards of AIDS following HIV-1 seroconversion in men carrying a given marker compared with all men not carrying that marker.[20, 24] Using these data, individual alleles or allele combinations associated with either extreme of disease progression were assigned an inte-

Table 1. Characteristics of 31 HIV-1 infected patients without antiretroviral therapy

Patient code	Sex age[a]	Year of diagnosis	Follow up after Dx[c]	Start of KRG	HIV-1 subtype	HLA class I typing[d]	TAP 2	HLA score
Patients with protective HLA allele (n=16)								
1	M9	1987	202	Nov-91	B	A2, 33 B44, 55 C1, 14	2.1/2.3	1
3	F37	1988	188	Dec-91	B	A2, 30 B14, 38 C7, 8	2.2/2.4	2
4	M29	1988	181	Dec-91	CRF02_AG	A2, 33 B38, 44 C7, 14	2.1/2.3	1
5	M33	1989	174	Oct-92	CRF02_AG	A3, *24* B44, 51 C5, 14	2.2/2.3	1
10	M23	1990	169	Nov-91	B	A2, 26 B27, 54 C1, -	2.2/2.3	2
12	M28	1990	161	Dec-91	B	A11, 33 B27, 44 C2, 7	2.2/2.3	1
13	M22	1990	160	Nov-92	B	A2, 26 B61, 62 C8, 9	2.1/2.4	2
15	M20	1990	170	Feb-93	B	A2, *24* B7, 27 C1, 7	2.2/2.3	0
18	M28	1989	184	Dec-91	B	A24, - B51, 52 C12, 14	2.2/2.4	2
22	M35	1992	144	Nov-92	B	A11, 26 B55, 62 C1, 8	2.2/2.3	2
23	M11	1992	147	Aug-00	B	A30, 32 B14, 44 C5, 8	2.2/2.3	3
25	M23	1992	141	No KRG	B	A*24*, - B39, 51 C7, 14	2.2/2.3	1
27	M16	1992	133	Feb-92	B	A11, 32 B44, 62 C4, 5	2.2/2.3	1
28	M22	1992	141	Jun-93	B	A2, 30 B14, 35 C8, 9	2.2/2.3	2
29	M21	1992	134	Apr-93	D	A26, 33 B44, 55 C12, 14	2.1/2.4	2
30	M30	1992 [b]	143	Mar-93	B	A2, 26 B62, - C8, 9	2.2/2.4	2
Patients without protective HLA allele (n=15)								
2	F32	1988	182	Sep-92	Untyped	A2, 33 B13, 44 C6, 7	2.3/2.3	0
6	M19	1989	158	No KRG	B	A2, *24* B67, 52 C7, 12	2.1/2.4	-1
7	M21	1989	173	Dec-91	B	A*24*, 11 B39, 56 C1, 7	2.2/2.3	-1
8	M25	1989	167	No KRG	B	A2, 33 B58, *60* C4, 10	2.1/2.4	-1
9	M27	1990	162	Jan-92	B	A2, *24* B62, 54 C1, 10	2.2/2.3	-1
11	M32	1990	164	Dec-91	CRF01_AE	A24, 33 B58, 60 C4, 10	2.2/2.4	0
14	M26	1990	161	Apr-92	B	A2, *24* B62, 54 C7, 10	2.2/2.3	-1
16	M11	1991	144	May-93	B	A*24*, - B7, 54 C1, 7	2.1/2.3	-1
17	M14	1991	153	May-93	B	A2, 24 B13, 62 C9, 10	2.2/2.4	0
19	M8	1989 [b]	166	No KRG	B	A1, *24* B39, 52 C7, 12	2.1/2.3	-1
20	M16	1989 [b]	169	Oct-92	B	A2, 31 B7, 46 C1, 7	2.2/2.3	0
21	M19	1992	145	May-93	B	A2, - B40, 48 C9, 10	2.2/2.3	0
24	M29	1992	132	No KRG	B	A*24*, 33 B44, *60* C7, 10	2.1/2.3	-2
26	M5	1992	141	No KRG	B	A2, *24* B40, 61 C10, -	2.2/2.3	-1
31	F26	1993	134	Nov-96	B	A11, 24 B52, 62 C4, 12	2.2/2.4	0

[a] Age at the time of HIV-1 diagnosis.
[b] Year of HIV-1 infection in 3 patients.
[c] Follow up means duration from HIV-1 diagnosis to date on outcome.
[d] Underlined and italic alleles denotes protective (+1) and adverse antigens (-1), respectively.

ger value, with -1 indicating an association with rapid progression and +1 indicating an association with long-term non-progression.[24, 29] Among the protective alleles were B27, B51, B57, A25 with TAP2.3, A26 with TAP2.3, A32 with TAP2.3, B18 with TAP2.3,[20, 24, 29] B14, Cw8, and Cw14.[30] Among the alleles associated with rapid progression were B37, B49, A28 with TAP2.3, A29 with TAP2.1, B8 with TAP2.1, A23 with out TAP2.3, A24 with TAP2.1 or TAP2.3, B60 with TAP2.1 or TAP2.3,[20, 24, 30] B35 with Cw4.[29] All other alleles received a value of zero. For each

individual, the HLA score profile was calculated as the algebraic sum of the values given to each allele (Table 1).

CD4 and CD8 T cell counts

After staining PBMC with phycoerythrin (PE) and fluorescein isothiocyanate (FITC)-conjugated antibodies against CD4 and CD8 antigens (Simultest reagent, Becton Dickinson, San Jose, CA, USA)[17,18] CD4 T and CD8 T cells were determined by FACScan (Becton-Dickinson) flow cytometer.

Table 2. Comparison of outcome over 10 years between 2 groups

Patient code	CD4 T cell (/μL)		Date on outcome	Duration[a] (months)	KRG (g) supplied[b]	Annual decrease in CD4 T cell (/μL)	Plasma HIV-1 RNA copy (/ml)
	baseline	outcome					
Group A (n=16) with consistent and significant KRG-intake							
1	466	124	Mar-04	150	> 9,720	27	26,900
4	707	417	Oct-03	142	> 8,796	24	821
7	319	140	Jan-04	145	5,076	15	162,000
9	409	216	Jan-02	123	> 4,026	19	97,800
10	304	165	Mar-04	149	> 19,302	11	4,500
12	537	408	May-03	137	12,822	11	116,000
14	737	578	Mar-03	131	> 3,792	15	698
15	635	332	Mar-04	133	> 6,600	27	104,000
18	495	519	Aug-03	140	> 9,396	2	17,800
21	241	212	May-04	144	> 6,510	2	14,600
22	420	130	Feb-04	144	> 12,000	24	88,600
23	446	424	May-04	140	3,420	2	4,000
27	700	643	Mar-03	133	7,776	14	111
29	344	348	Feb-04	130	> 8,640	0	35,800
30	581	324	Mar-04	132	> 5,880	23	31,900
31	592	454	May-04	90	> 5,760	18	5,750
Group B (n=15) with a little or no KRG-intake							
2	250	3	Jan-02	137	< 500	22	ND[c]
3	986	42	Jan-99	120	< 1,920	94	ND
5	893	178	Feb-01	100	2,406	83	345,654
6	945	20	Mar-01	141	0	79	90,467
8	471	18	Feb-99	109	0	50	ND
11	685	360	Dec-03	142	3,120	27	3,710
13	1088	187	Oct-00	115	< 1,410	94	256,250
16	576	26	Aug-02	135	> 360	49	ND
17	629	261	Feb-04	153	< 1,080	29	35,900
19	337	178	Jul-00	108	0	18	17,000
20	453	26	Nov-99	100	< 1,500	51	366,197
24	767	280	Apr-02	119	0	49	ND
25	589	502	Nov-03	130	0	8	11,500
26	966	152	Nov-03	136	0	72	209,000
28	315	179	Oct-03	130	< 750	13	ND

[a] Duration between baseline and outcome.
[b] > means there was additional purchase of KRG and < means that adherence was poor.
[c] ND, not determined.

Statistical analysis

Data are expressed as mean ± standard deviation. Statistical significance was estimated by correlation coefficient among 4 variables (amount of KRG, AD, HIV-1 RNA copy, and HLA score) and Chi-square test or Fisher's exact test between 2 groups using a statistical package program from CATS (Seoul, Korea).

RESULTS

HLA genotyping

We performed HLA class I genotyping in the 31 patients and scored the HLA genotypes as explained in Materials and Methods. We found that 16 patients had at least one protective allele, whereas 15 did not have any protective allele (Table 1). Six patients each had C8 and C14, 5 had A26, 3 each had B27 and/or B14, and 2 each had A32 and B51. Frequencies of these 7 protective alleles among 31 patients did not show significant difference compared to those in 199 normal controls without HIV-1 infection in Korea (Table 3). For adverse antigens, 11 and 2 patients had A24 and B60, respectively. The HLA score in each patient ranged from +3 to -2, with the mean score in the 31 patients being 0.48 ± 1.31.

Table 3. Comparison of frequency of protective HLA allele between 31 HIV-1 infected patients and 199 normal controls without HIV-1 infection

HLA allele	Control (%) (n=199)	HIV patient (%) (n=31)	P-value
A26	22 (11)	5 (16.1)	> 0.05
A32	2 (1)	2 (6.5)	0.08
B27	12 (6)	3 (9.7)	> 0.05
B14	9 (4.5)	3 (9.7)	> 0.05
B51	30 (15)	2 (6.5)	> 0.05
C8	37 (18.6)	6 (19.4)	> 0.05
C14	48 (24.1)	6 (19.4)	> 0.05
Total	160 (80.4)	27 (87.0)	> 0.05

Correlation among KRG-intake, plasma HIV-1 RNA copy, CD4 T cell count, and HLA score

Although the mean follow-up period from HIV-1 diagnosis to the latest CD4 T cell count, was 159 ± 18 months, the duration from first CD4 T cell count after starting KRG treatment, or first CD4 measurement in patients not taking KRG, to the latest CD4 cell count was 130 ± 16 months (Table 2). Baseline CD4 T cell count averaged 577 ± 231/μL and was above 200/μL in all patients, declining to 253 ± 178/μL after 130 ± 16 months ($P < 0.001$). This corresponds to an annual decrease of 30 ± 29 cells/μL. This rate of AD in patients with significant amount of KRG-intake is much lower than the natural decrease (70/μL) observed in the HIV-1 infected Korean population.[31]

From table 2, we analyzed whether there was any significant correlation among the amount of KRG ingested, HLA score, and AD over 130 ± 16 months period (Fig. 1). We observed significant correlations between KRG-intake and AD ($r = -0.53$, $P < 0.01$) (Fig. 1A) and between KRG-intake and HLA score ($r = 0.49$, $P < 0.01$) (Fig. 1B). To determine whether there was any significant correlation between the amounts of KRG-intake and plasma HIV-1 RNA copy, we also analyzed these correlations. We observed significant correlations between KRG-intake and HIV-1 RNA copy ($r = -0.35$, $P < 0.05$) (Fig. 1C) as well as between viral load and AD ($r = 0.76$, $P < 0.001$) (Fig. 1D).

Effects of KRG-intake and HLA haplotype

We wanted to determine the effect of protective HLA alleles on viral load and CD4 T cells in HIV-1 infected individuals. The 31 patients were divided into 2 groups according to the presence or absence of protective HLA alleles (Table 1). Coincidently, we found that the 16 patients with at least one protective HLA allele received more KRG for 133 ± 13 months, whereas the 15 patients who did not have any protective HLA allele received less KRG for 128 ± 19 months ($P < 0.01$). Although CD4 T cell counts decreased significantly in both groups over 10 years, the decrease tended to be lower (AD of 26.5/μL) in the 16 patients with a protective allele than in the 15 patients without any protective allele (AD of 34/μL). However, there was no significant correlation between HLA score and AD ($P > 0.05$, Fig. 1E). Plasma viral RNA was similar in both groups ($P > 0.05$, Fig. 1F). These results indicate that despite a significant difference in the amount of KRG-intake, HLA haplotype alone did not have a significant effect on AD or viral load.

In the very same way, we also divided the 31 patients according to the amount of KRG ingested (Table 2). Comparison of clinical factors between 2 groups is summarized in table 4. The 16 patients taking the higher amount of KRG received 8,478 ± 4,197 g KRG for 137 ± 15 months, whereas the 15 patients taking less KRG received 870± 1,007 g of KRG for 125 ± 16 months. Although CD4 T cell count decreased significantly in both groups over 10 years ($P < 0.001$), the level of decrease was significantly lower in the former (AD of 14/μL) than that in the latter (AD of 49/μL, $P < 0.001$). Plasma viral load was also significantly

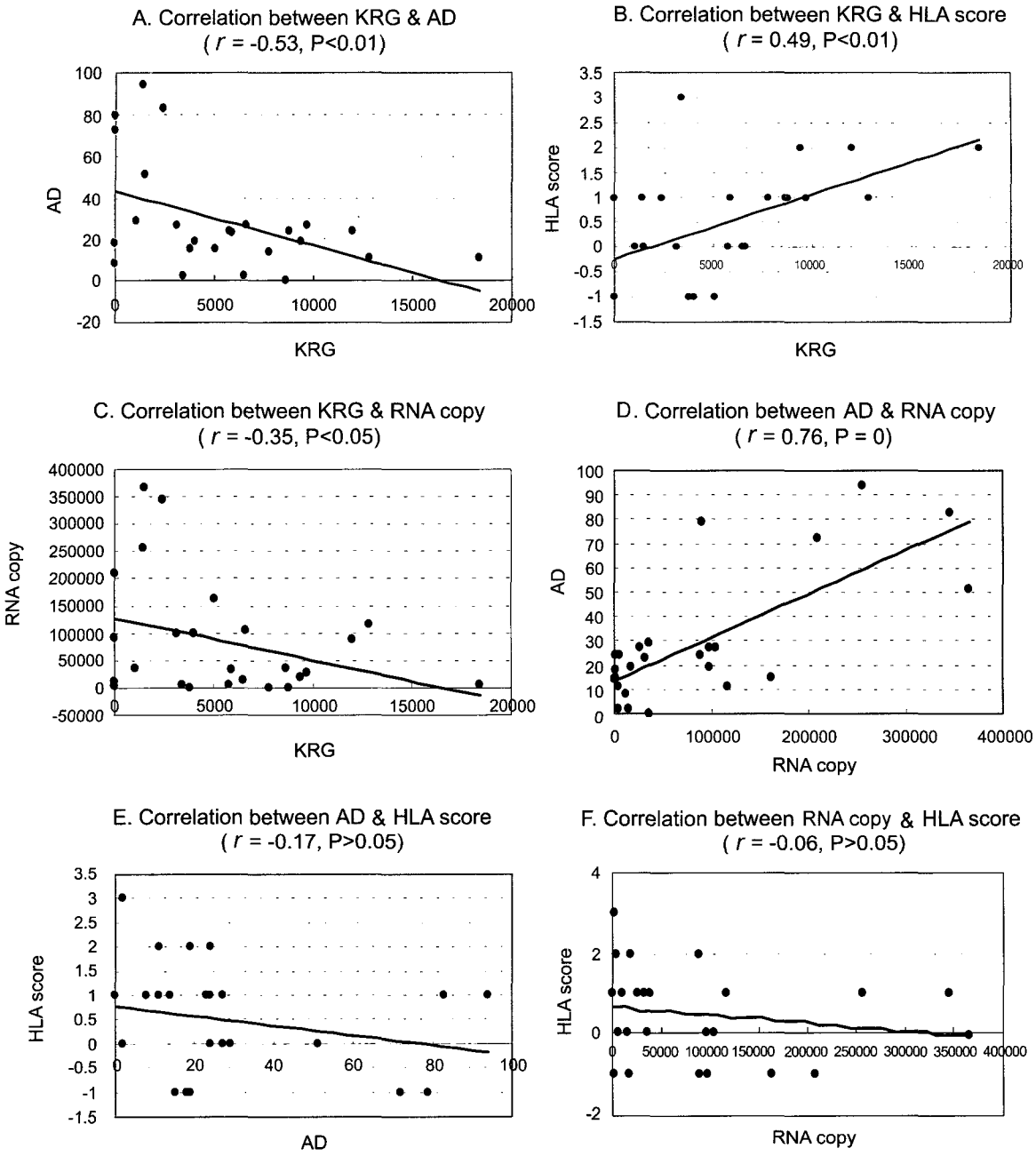

Fig. 1. Correlations among the amount of KRG-intake, annual decrease in CD4 T cells (AD), plasma HIV-1 RNA copy, and HLA score There were significant correlations not only between HIV-1 RNA copy and AD (D) but also among KRG-intake and AD (A), anc HLA score (B), and HIV-1 RNA copy (C). In contrast, there were no significant correlations between HLA score and AD (E) as wel as between HLA score and HIV-1 RNA copy (F) in this small size of study with 31 patients.

lower in the former (44,455 ± 51,597 copies/ml) than in the latter (158,863 ± 139,304 copies/ml) ($P < 0.01$). From these results, it is indicated that consistent KRG-intake seems to contribute more in lowering AD and viral load than HLA alleles.

We also observed a significant difference in HLA score between the two groups (0.87 ± 1.26 vs. 0.07 ± 1.28, $P < 0.05$). The number of patients whose CD4 T cells decreased to below 200/μL was significantly less in group A (4/16) than in group B (11/15) ($P < 0.05$) (Table 4). Comparison of these two groups suggests that, although there was no significant correlation between HLA score alone and other variables in this small size of study with 31 patients, high HLA score together with KRG may have additive effects in improving all clinical parameters measured.

Table 4. Summary of comparison of outcome over 10 years between 2 groups based on table 2

Variables	Group A	Group B	P-value
No. of patients	16	15	> 0.05
Duration (months)	137 ± 15	125 ± 16	> 0.05
Amount of KRG supplied (g)	8,478 ± 4,197	870 ± 1,007	< 0.001
HLA score	0.87 ± 1.26	0.07 ± 1.28	< 0.05
Baseline CD4 T cell (/μL)	497 ± 154	663 ± 269	< 0.05
Outcome CD4 T cell (/μL)	340 ± 164	161 ± 145	< 0.001
Total decrease in CD4 T cell	156 ± 118	503 ± 296	< 0.01
Annual decrease in CD4 T cell	14 ± 9	49 ± 30	< 0.001
Plasma HIV-1 RNA copy (/ml)	44,455 ± 51,597	158,863 ± 139,304	< 0.01
No. of patient with CD4 T cell <200/μL as outcome	4 (25)	11 (73)	< 0.05
No. of patient on HAART after outcome	4 (25)	11 (73)	< 0.05
No. of patient with admission after outcome	1 (6)	7 (47)	< 0.05

HAART; highly active antiretroviral therapy.

DISCUSSION

In the present study, we performed extended analysis of the effects of KRG-intake on important clinical parameters including HLA genotyping, CD4 T cells, AD, and RNA copy level as well as the number of patients who needed HAART treatment and hospital admission. We found that there was a strong positive correlation between KRG-intake and clinical parameters described above. In contrast, we did not observe such a strong correlation between protective HLA alleles alone and clinical parameters. The group of patients who took KRG and have protective HLA alleles showed significantly improved clinical parameters indicating a possible additive effect of KRG and presence of protective HLA alleles.

Defects in *nef* genes have been linked to nonprogressive infection. Rhesus monkeys experimentally inoculated with simian immunodeficiency virus carrying deletions in the *nef* gene have low viral loads and normal CD4 T cell counts and no signs of diseases.[32] Moreover, approximately 4% (3 out of 70) of the individuals in the Australian long-term nonprogressor (LTNP) cohort reported to be infected with viruses containing *nef* defective genomes[33] although there are many case reports on LTNP containing defective *nef* gene. In our recent study, we found that there is a strong association between KRG-intake and high frequency of gross deletions in the *nef* gene.[35] Interestingly, all 3 patients with the allele B27 in the present study revealed grossly deleted *nef* genes in consecutive samples, whereas 20 Australian LTNPs with HLA B27 did not show any deletion in the *nef* gene.[34] Ten out of 16 patients who belong to group A with significant KRG-intake revealed grossly deleted *nef* genes. Thus, the KRG-intake and/or the presence of protective HLA alleles may play a role in maintaining *nef* gene deleted viruses or deleting the *nef* gene although the mechanism is not clear.

Progression to AIDS is strongly associated with generalized activation of the immune system, manifested by elevated serum concentrations of neopterin, soluble IL-2-receptor, sCD8, and β_2-microglobulin, and with activation of a large proportion of CD8 T cells.[36] From the long-term studies with KRG, one of important findings was a significant decrease in serum sCD8[16] which is an immune activation marker physiologically secreted from CD8 T cells. In our pilot study,[16] patients treated with KRG or KRG plus zidovudine (ZDV) showed significant increases in CD8 T cell counts (22.8% compared to baseline) ($P < 0.01$) and significant decreases in sCD8 (13.8% compared to baseline) ($P < 0.05$). Moreover, the significant and consistent decrease in sCD8 (19.2%) was maintained as long as KRG was taken continuously ($P < 0.01$).[37] In the group assayed here, the decrease in sCD8 (34.5%) was even greater than those observed previously (13.8% and 19.2%). In addition, the pattern of continuous decrease of sCD8 in the HIV-1 infected individuals who had significant KRG-intake was different from the rebound phenomenon observed during ZDV monotherapy. Thus, the decrease in sCD8 may be indicative of a lower level of destruction of CD8 T cells in patients ingesting KRG and suggests that the latter agent is associated with prolonged maintenance of enhanced CTL activity.

Although the mechanism of ginseng is not well defined, it

is demonstrated that adaptogenic properties of ginseng are due to its effects on hypothalamic-pituitary-adrenal axis, resulting in elevated plasma corticotropin and corticosteroids levels.[29-30, 38] This action of ginseng might contribute a lot for suppressing hyperactivation of immune system. The important role of suppressing a hyper-immune state in preventing AIDS progression was recently demonstrated by a study that nonpathogenic SIV infection of sooty mangabeys is characterized by low level immune activation despite chronic high-level viremia compared to other species of monkey leading to AIDS progression.[39]

Our data show that as a single variable, the amount of KRG taken was more significant in improving clinical parameters of HIV infected patients than the HLA score, but that there was a significant correlation between KRG-intake and HLA score. Coincidently, patients with a higher frequency of protective HLA alleles took more KRG than patients with lower HLA scores although the frequency of protective HLA alleles in the 31 patients did not show a difference compared with that in normal individuals (Table 3). This suggests that the HLA haplotype also contributes to slowing the decrease in CD4 T cell count, although, in this small sample, it did not show statistical significance.

Despite the enormous efforts for developing AIDS vaccines for two decades, effective vaccines against HIV are not available yet. There are limitations in applying HAART chemotherapy to HIV patients in general. Considering the extreme difficulties in developing HIV vaccines and limitations of HAART, KRG-intake may provide an alternative and effective way of treatment for HIV-1 infected patients. In conclusion, despite our small sample size, we have shown that KRG-intake has a large effect on slowing the decrease in CD4 T cells and on plasma viral load in HIV-1 infected patients and that it may have an additive effect with protective HLA alleles.

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