International Journal of Biomedical and Pharmaceutical Sciences ©2012 Global Science Books

Ginseng in the Treatment of AIDS

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ABSTRACT

Despite introduction of highly active antiretroviral therapy, the AIDS pandemic continues to spread across the world. Although the development of an effective vaccine is urgently required, we still do not have any vaccine. In this regard, we need to look back towards alternative ways based on history and the recent scientific literature. Immunotherapy is currently receiving great attention as supporting treatment modalities in the management of cancer and AIDS patients whose immune function is compromised. Ginseng has long been used to maintain the vitality of man in the Orient. Recent studies have shown that ginseng has significant potential as an immune modulator and adjuvant. We have reported the beneficial effects of Korean red ginseng (KRG) in HIV-1-infected individuals since 1991. Several patients have remained healthy for up to 23 years in the absence of HAART. Of note, most patients treated with KRG reveal significantly high frequency of genetic defects in HIV-1 genes of as well as attenuation of chronic immune activation. A series of our data and literature show the possibility that ginseng could be a safe and effective medicine for treating AIDS patients.

Keywords: genetic defects, HIV-1, Korean red ginseng

CONTENTS

INTRODUCTION

The introduction of a highly active antiretroviral drug therapy (HAART) has proven effective in the treatment of human immunodeficiency virus (HIV)-1-infected patients (Ho *et al*. 1995; Wei *et al*. 1995). HAART alone, however, cannot eradicate the virus in the reservoirs (Chun *et al*. 1997; Finzi *et al*. 1997; Hendel *et al*. 1999). With regard to immunopathogenesis, production of Th1 cytokines is gradually reduced in HIV-1-infected patients (Chun *et al*. 1998, 1999). Thus, the key immune modulator in cell-mediated immunity, interleukin (IL)-2 has recently been tried in combination with HAART (Chun *et al*. 1999). Although IL-2 therapy significantly increases the number of circulating CD4 T cells, it has also many limitations because of severe adverse effects. Thus, a new modality with safety is required for more effective therapy of AIDS. Despite the discouraging news of expanding epidemics and the many biological changes imposed by HIV, there is no report on an effective vaccine. Considering the low transmission rate of HIV in settings of sexual transmission or needle stick injuries, a vaccine that induces even a modest improvement in antiviral defenses may have a profound impact on the transmissibility of HIV (Womack *et al*. 2004). Regarding pathogenesis, HIV infection is a kind of chronic wasting disease accompanied by a chronic generalized immune activation state that is significantly attenuated in simian immunodeficiency virus$_{SM}$ (Silvestri *et al*. 2001).

Ginseng, a medicinal herb, has long been used to maintain the vitality of man in the Orient because its medicinal properties have been recognized through experience for thousands of years. Famous books on Oriental medicine (Shen Nong Ben Cao Jing in China; Dongeuibogam in Korea, 1610) say that long-term intake of ginseng prolongs life. We have treated HIV-infected individuals with Korean red ginseng (KRG) since late 1991. Our data shows that long-term intake of KRG might attenuate the HIV-1 gene as well as its clinical usefulness.

Received: 18 April, 2010. Accepted: 18 April, 2011.

Invited Review

In this context, our clinical experience over 18 years indicate that KRG could be a good alternative medicine in the treatment of HIV individuals and related scientific findings also show an immunological basis for its usefulness.

HOW DOES GINSENG WORK IN HUMANS?

In the Orient, ginseng (*Panax ginseng* C. A. Meyer) especially has been used as a medicine for more than 2000 years (Li *et al*. 1973). At present, ginseng ranks as having the second highest annual sales of any herbal medicine in the USA market place and is used world-wide (O'Hara *et al*. 1998). Since the late 1960s, many studies have been performed to identify the active ingredients of ginseng and their functions. Ginseng is considered an adaptogenic agent, which enhances physical performance, promotes vitality and increases resistance to stress and aging, and possesses immunomodulatory activity (Singh *et al*. 1984; Scaglione *et al*. 1990; See *et al*. 1997). The adaptogenic properties of ginseng are believed to be due to its effects on the hypothalamic-pituitary-adrenal axis (Hiai *et al*. 1979; Fulder *et al*. 1981; Nocerino *et al*. 2000). Its immunomodulatory activity means to improve defense systems that can overcome tumor and microbial infection.

As the front line of host defense, the importance of innate immunity in AIDS pathogenesis is being highly recognized recently as we realize that adaptive immunity alone such as cytotoxic T lymphocyte activity or a neutralizing antibody against HIV cannot control HIV infection. It is well known that ginseng augments innate immunity, especially on natural killer cell activity as well as adaptive immunity. NK function (15 ± 7) in AIDS patients with a CD4 count < 200/μl is significantly lower (113 ± 20) than in normal controls ($p<0.001$). The presence of ginseng extract significantly enhanced NK-function by peripheral blood mononuclear cells from normal controls at concentrations of >10 μg/ml and AIDS at 1 μg/ml in a dose-dependent manner (See *et al*. 1997).

P. ginseng extract also increased cell-mediated immune functions, such as CD4 T helper subset, in man (Scaglione *et al*. 1990). In the multicentre, two-arm, randomized, placebo-controlled, double-blind investigation related to effect of ginseng on common cold mobidity, ginseng also induced a higher immune response in vaccination against influenza, and raised antibody titres, compared to the placebo group (Scaglione *et al*. 1996). NK activity levels 2-3 months after vaccination with ginseng treatment were nearly 2-fold higher than the placebo group. *P. ginseng* also stimulated basal NK cell activity and helped recovery of NK function in cyclophosphamide-immunosuppressed mice (Kim *et al*. 1990). Ginseng was a safe and potent adjuvant, when used for immunisation against *S. aureus* and parvovirus (Hu *et al*. 2003; Rivera *et al*. 2003).

P. ginseng increases the resistance of athymic rats to *P. aeruginosa* lung infection (Song *et al*. 2003) as well as interferon-gamma (IFN-γ) and interleukin-12 production in infections with intracellular microorganisms such as *Listeria monocytes*, mycobacteria and *Leishmania* parasites and extracellular chronic infections such as *P. aeruginosa* (Song *et al*. 1997; Larsen *et al*. 2004).

Production of TNF-alpha and IFN-γ as well as the expression of IFN-beta and inducible nitric oxide synthase mRNAs was induced by ginseng extract (GE) in spleen cells and peritoneal macrophages from C3H/HeN mice. These findings suggest that GE can enhance innate immunity through production of proinflammatory cytokines via TLR-4 (Nakaya *et al*. 2004).

P. ginseng could reduce cell damage, especially damage to DNA molecules, against radiation exposure in mice and play a role in the repair or regeneration process of damaged cells (Kim *et al*. 1993; Lee *et al*. 2005).

Based on these findings, ginseng has been recognized as a representative biological response modifier as well as an adjuvant (Song *et al*. 2009). This suggestion was also supported by a report of Howard that ginseng lowers the incidence of upper respiratory tract infections, because it reduced cortisol production and increased the relative effectiveness of available DHEA. Therefore, many researchers are interested in the therapeutic effect of *P. ginseng* against cancer as well as AIDS (Howard 2006).

WHAT ARE THE BIOACTIVE CONSTITUENTS IN GINSENG?

Ginseng usually refers to the dried of several species in the plant Panax sp. (Family Araliaceae). Three major commercial ginseng are *P. ginseng* C.A. Meyer (Korean ginseng or Asian Ginseng), *P. quiquefolium* (North American Ginseng) and *P. notoginseng* (Chinese Ginseng) (Kennedy *et al*. 2003; Lee *et al*. 2005). The steamed and dried *P. ginseng* is called red ginseng. It is frequently used as a herbal medicine in Asian countries (Kitagawa *et al*. 1983; Kim *et al*. 2000; Kwon *et al*. 2001). *P. ginseng* is the most commonly used and extensively researched species. Approximately 200 substances, such as ginsenoside, polysaccharides, polyacetylenes, peptides and amino acids, have been isolated from Korean ginseng (Attele *et al*. 1999). Nevertheless, its major components are ginseng saponin (such as about 40 ginsenosides) and polysaccharides (such as ginsans, panaxans).

The major components of raw ginseng or dried ginseng (named as a white ginseng) are ginsenosides Rb1, Rb2, Rc and Rf, and macromolecule polysaccharides such as panaxans B (1800 KDa) and K (130 KDa). However, those of red ginseng are ginsenosides Rg3 and Rh2, and acidic polysaccharides, such as panaxans M (800KDa) and T (11 KDa), which are produced by heat process. The heat process in raw ginseng increased acidic polysaccharides (Konno *et al*. 1984; Lee *et al*. 1997; Belogortseva *et al*. 2000; Kim *et al*. 2003).

Investigating the efficacy of ginseng therapy is a complex process, because ginseng contains many constituents. Although pharmacological activities of all components were not clarified, the bioactive constituents of ginseng are considered to be ginseng saponin and polysaccharides. The ginsenosides have been reported to show anti-tumor (Wakabayashi *et al*. 1998; Chang *et al*. 2003; Helms *et al*. 2004), anti-diabetic (Yokozawa *et al*. 1985; Xie *et al*. 2005), anti-inflammatory activity (Park *et al*. 2004), anti-allergic (Choo *et al*. 2003; Park *et al*. 2003), endothelium-independent aorta relaxation (Kim *et al*. 1999) adjuvant-like (Wu *et al*. 1992), and immunomodulating effects (Rivera *et al*. 2003; Lee *et al*. 2004). The polysaccharides have been reported to show anti-inflammatory (Ahn *et al*. 2006), antidiabetic (Ng and Yeung 1985; Belogortseva *et al*. 2000), antitumor (Shin *et al*. 2004), and immunostimulating effects (Konno *et al*. 1984), etc. Recently, the importance of inflammation in association with AIDS pathogenesis has highly been recognized. We also would like to put a high value of KRG intake in regard to anti-inflammation-effect of ginseng.

GINSENG SAPONIN AS AN IMMUNOMODULATING AGENT

Ginseng saponins, ginsenosides, are triterpene glycosides (Tanaka *et al*. 1972). These ginsenosides can be categorized into three groups depending on their aglycones: protopanaxadiol, protopanaxatriol and oleanolic acid. *P. notoginseng* saponin is consisted of some ginsenosides and notoginenosides (Zhu *et al*. 2004). Ginsenosides have been reported to exhibit potent biological activities such as immunomodulating, antidiabetic, anti-tumor effects, etc. In detail, saponins from *P. ginseng* and *P. notoginseng* potently stimulate cellular and humoral immune responses (Song *et al*. 2007; Sun *et al*. 2009). Ginsenoside Rb1, which is the richest constituent in *P. ginseng*, induced serum-detectable amounts of IL-4 and IL-10 as early as 24 h after primary vaccine injection in mice (Biondo *et al*. 2008). Five weeks after booster, immune lymphocytes was still producing large amounts of cytokines including IFN-γ, IL-2, IL-4, IL-

10 and TNF-α. The Rb1 adjuvanted vaccines stimulated similar titres of antigen specific IgG. The ginsenoside Rb1 also had the strongest adjuvant effects, when used for immunisation against *S. aureus* (Hu *et al*. 2003). Ginsenosides Rb1 as well as Rg1 are potent adjuvants inducing higher or similar antibody titres than the vaccine adjuvanted with alum hydroxide alone (Rivera *et al*. 2003, 2005). Ginsenoside Rg1 increases the proportion of Th cells among the total number of T cells and promotes IL-2 gene expression in murine splenocytes (Lee *et al*. 2004). Ginsenoside Rg1 had no mitogenic effects on unstimulated CD4 T cells. The ginsenoside Rg1 is a desirable agent for enhancing CD4 T-cell activity, as well as the correction of Th1-dominant pathological disorders. *P. ginseng* intake increases the immune response by induction of interleukin-12 production (Larsen *et al*. 2004).

In a cellular and humoral immunity study of ginsenosides-Rb1, -Rd, notoginsenosides-K, and -R4, the haemolytic activity was K > R(4) > Rb(1) > Rd and mitogen- and ovalbumin-induced splenocyte proliferation activity was Rd > Rb1 > K > R4 (Sun *et al*. 2005). Adjuvant potentials of ginsenoside Rd on antibody responses were higher than those of other three ginsenosides. Ginsenoside Rd also significantly enhanced the production of the Th1 and Th2 cytokines in ovalbumin-immunized mice. Among seven protopanaxatriol-type ginsenosides (protopanaxatriol, protopanaxadiol, ginsenoside-Re, -Rg1, -F 1, -Rh1, 20R-Rh1), ginsenoside-Rh1 and 20R-Rh1 induced a Con A-induced type 1 cytokine pattern by increasing the production of IL-12, the expression of IFN-γ, T-beta and enhancing NF-κB DNA binding activity (Yu *et al*. 2005). Ginsenoside R2 and notoginsenoside R1 are potent immunologic adjuvants with low hemolytic effect (Sun *et al*. 2006). These findings suggest that ginsenosides can modulate cellular and humoral immunities.

GINSENG POLYSACCHARIDE AS A POTENT IMMUNOSTIMULATING AGENT

Immunostimulating agents are currently receiving great attention as supporting treatment modalities in the management of cancer and AIDS patients whose immune function is compromised. Polysaccharides as immunostimulating agents from various sources, including higher plants, have aroused great interest in recent years. Many of these polysaccharides, such as lentinan, krestin and ginsan, have profound effects on the immune system and are relatively nontoxic (Han *et al*. 2005). Water-soluble polysaccharides from *P. ginseng* have a number of effects on immune and host defense functions: they significantly increased lysosomal phosphatase activity and phagocytic index of peritoneal macrophages through the production of reactive oxygen intermediates (nitric oxide (NO) and hydrogen peroxide (H_2O_2)) (Wang *et al*. 2001; Lim *et al*. 2004).

Ginseng polysaccharide activates macrophages against *Candida albicans* (Tomoda *et al*. 1994), potentiates anticomplement activity (Tomoda 1993), induces IFN-γ and TNF-α production in lymphocytes and peritoneal macrophages (Jie *et al*. 1984; Gao *et al*. 1996), stimulates phagocytosis in polymorphonuclear leucocytes (Hu *et al*. 1995), stimulates natural killer-cell activity (Kim *et al*. 1990) and activates components of cell-mediated immunity (Scaglione *et al*. 1990) including IL-2 expression (Ma *et al*. 1995). It has also been shown to reduce bacterial load and lung pathology in animal models of cystic fibrosis (Song *et al*. 1994) and to exert potent gastric cytoprotective and antiulcer effects (Sun *et al*. 1991; Kiyohara *et al*. 1994).

Acidic polysaccharides (Ginsan) from *P. ginseng* induce the expression of IL-2, IFN-γ, IL-1-α, and GM-CSF, as well as lymphokine-activated killer (LAK) and CD8+T cells (Kim *et al*. 1998). The anti-septicemic effect of a polysaccharide from *P. ginseng* in C57BL/6J mice was observed by increased NO production from stimulated macrophages (Lim *et al*. 2002). The phagocytic activity of macrophages treated with ginsan was significantly enhanced against *S. aureus*. Treatment with ginsan significantly reduced the expression of TLR 2 and the adaptor molecule MyD88, which was greatly increased in septic macrophages, *in vitro*. Similarly, the expression of phospho-JNK1/2, phospho-p38 MAPK, and NF-kB was also decreased in the same culture system (Ahn *et al*. 2006). However, ginsan markedly downregulated the production of proinflammatory cytokines, such as TNF-α, IL-1β, IL-6, IFN- γ, IL-12, and IL-18, in mice.

The polysaccharide fraction from *P. quinquefolium* also enhances immune responses: it increased immunoglobulin and cytokines production (Wang *et al*. 2004). In addition, it significantly increased IL-2 and IFN-γ productions in Con-A-induced spleen cells in a dose-dependent manner in the murine model.

Red ginseng acidic polysaccharide (RGAP), having B cell-specific mitogenic activity, induced the secretion of IL-6 in spleen cells in a concentration-dependent manner. RGAP also restored the immune responses, such as splenocyte proliferation and NK cell activity, suppressed by paclitaxel or cyclophosphamide (Shin *et al*. 2004; Du *et al*. 2008). Interestingly, acid polysaccharides of *P. ginseng* induce the expression of IL-2, IFN-γ, IL-1α, and GM-CSF, as well as LAK cells and CD8+T cells more than other ginseng polysaccharides (Cho *et al*. 1994; Kim *et al*. 1998; Wang *et al*. 2001).

The immunomodulating activity of polysaccharides is a common feature of several species of ginseng (Chinese ginseng *P. notoginseng*, American ginseng *P. quinquefolium*, and Korean ginseng *P. ginseng*) although the structure of ginseng polysaccharides has not been clarified and their activity is significantly different with regard to HIV pathogenesis.

GINSENG AND ANTIVIRAL ACTIVITY

Several proteins isolated from ginseng revealed anti-reverse transcriptase (RT) or anti-protease of HIV-1 (Wang *et al*. 2000; Zhang *et al*. 2002; Wei *et al*. 2009). Quinqueginsin has been isolated from the roots of *P. quinquefolium*. This protein displays a variety of biological activities. It possessed ribonucleolytic activity toward yeast tRNA and specific activity toward poly C. An inhibitory action was expressed toward HIV-1 RT. This action was potentiated after chemical modification with succinic anhydride (Lam *et al*. 2002). A xylanase with a molecular weight of 15 kDa inhibits HIV-1 RT (McElhaney *et al*. 2004).

EFFECTS OF KRG IN AIDS PATIENTS

Except for our experience, there is no clinical study with ginseng for HIV-1 infected individuals although American ginseng does not alter ZDV pharmacokinetics but reduces oxidative stress markers (Lee *et al*. 2008). Our clinical studies in HIV-1-infected individuals have been done with KRG which was manufactured by steaming under pressure and drying. During the process of manufacturing, there are great changes in the constituents; 12 specific ginsenosides including Rg3 and maltol belong to red ginseng only, and red ginseng has more antioxidants, and an increase in the Browning reaction, and a high content of acid polysaccharides (4-7%) compared to 0.6-0.8% in white ginseng (Nam *et al*. 1996). It is generally accepted that the effects of red ginseng are superior to white ginseng (Matsuda *et al*. 1987). The KRG used in our studies is a commercial product which was prepared from 6-year-old roots by Korea Ginseng Corp. A daily dose for our studies was 5.4 g and patients were told to take six capsules (300 mg/capsule) orally, three times daily. Daily 5.4 g is double the recommended dose. For females, we strongly recommend that the dose must be lessened to around 2.7 g by our long-term experience.

Six-month pilot study: KRG attenuates chronic immune activation

We have treated HIV-1-infected patients with KRG, alone or in combination with zidovudine (ZDV;the first approved antiretroviral drug) from late 1991 (Cho *et al*. 1994, 1996, 2002). A 6 month pilot study consisting of 4 arms showed a significant increase in CD4 T cell percentage in KRG (n = 23), ZDV (n = 29), combination of KRG and ZDV arms (n = 16), whereas significant decrease was observed in control group (n = 24) (**Fig. 1A**). Contrary to our expectation, CD8+ T cell percentage also significantly increased in both KRG ($p < 0.01$) and combination ($p < 0.05$) arms compared with mild increases in the other 2 arms (**Fig. 1B**). The increase in CD4 T cells by ginseng intake in the healthy group was also previously reported by another group although CD8 T cell count did not change (Scaglione *et al*. 1990). We measured soluble CD4 (sCD4) and CD8 antigen (sCD8) in sera by 3 months. Interestingly, sCD8 significantly decreased in both KRG and combination arms, whereas it mildly increased in the other 2 arms. However, sCD4 did not show any significant change in the 4 arms. With regard to its antiviral effect, p24 antigen decreased a little in both arms of the KRG treatment in contrast to a rebound phenomenon in ZDV. The decrease in sCD8 was compatible for the increase in CD8 T cells in arms with KRG treatment (**Fig. 2**). We thought the decrease in sCD8 in sera is very important because it is physiologically released from CD8+ T lymphocytes (CTL) and a marker indicating the immune activation state. A decrease in sCD8 was consistently observed and maintained over 6 years up to the final measure, whereas in the ZDV arm, it showed a rebound phenomenon. Thus, the study has been continuously conducted although there were several interruptions of 4-5 months between the pilot study and the 2nd term, between the 2nd and 3rd, and between the 3rd and 4th terms, and so on. However, some patients who had felt the effect of KRG intake took it following personal purchase during the lack of KRG supply. Patients 90-05 and 88-17 belonged to this example (Cho *et al*. 2006, 2009).

Ginsenosides appear to be responsible for most of the activities of ginseng including vasorelaxation, antioxidation, anti-inflammation and anticancer.

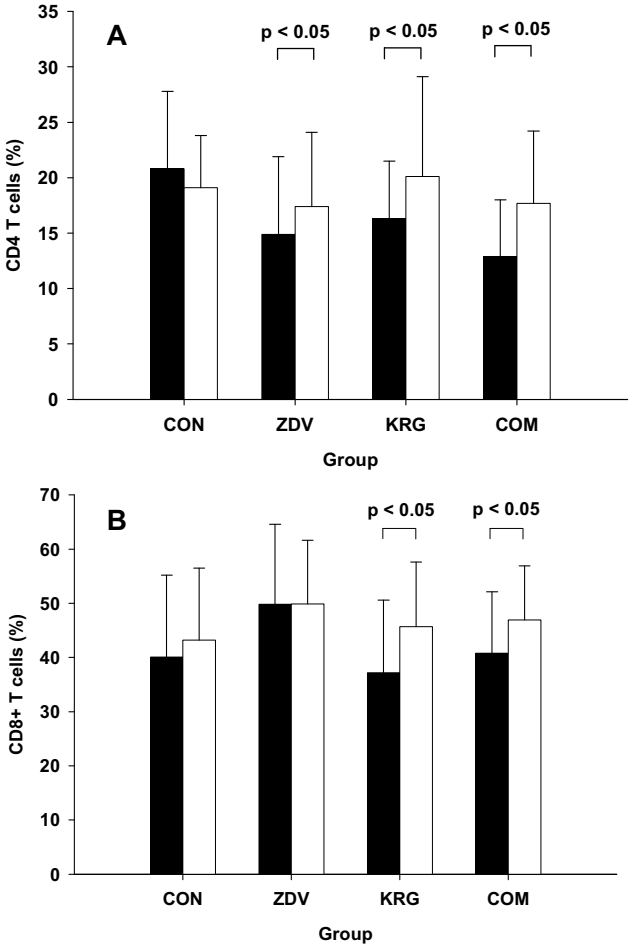

Fig. 1 (**A**) Comparison of change of CD4+ T cells for 6 months in 4 groups. CD4 T cell percentage in ZDV, Korean red ginseng (KRG) and COM groups significantly increased whereas it decreased a little in control group. (**B**) Comparison of change of CD8+ T cells for 6 months in 4 groups. CD8 T cell percentage significantly increased in KRG and COM groups only).

Ginseng might affect the HIV-1 *env* gene

Statistical analysis on the changes in CD4 T cells in 1996 showed that KRG intake has beneficial effects in HIV-1-infected patients. Thus, we questioned whether KRG intake could affect the HIV gene *in vivo* if our data were true over 5 years. At that time, there was no information on the HIV-1 gene in Korean patients. As in other countries, as the first target gene, we determined the *env* gene which shows the highest variation rate. We determined it in 65 patients (Cho *et al*. 1997). Among them, 40 patients were followed-up over 60 months by CD4 T cell measurement. Data analysis showed a significant inverse correlation between the decrease in CD4 T cell and the duration of KRG intake whereas there was no such correlation between CD4 T cells and ZDV. Above all, intrapatient variation of amino acids in 44 patients showed a significant inverse correlation with the months of KRG intake (**Fig. 3**). In other words, we could interpret that long-term intake of KRG slows the variation rate in the *env* gene in patients treated with KRG for a prolonged period. We thought that this phenomenon is very implicit with regard to HIV's intrinsic nature.

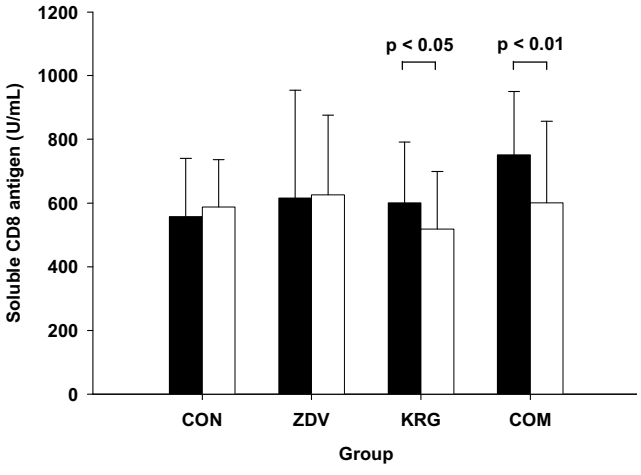

Fig. 2 Change of soluble CD8 antigen (sCD8) for 6 months in 4 groups. sCD8 significantly decreased in both KRG and COM groups only. Interestingly, these data are compatible with the change of CD8+ T cells in KRG and COM groups in **Fig. 1B** (Cho *et al*. 1996).

Delayed development of resistance mutation to ZDV

In Korea, ZDV monotherapy was introduced in early 1991 to treat HIV-1-infected patients and was the only antiretroviral therapy until early 1997 (Cho *et al*. 1993, 1996, 2002). It is well known that the effects of ZDV monotherapy were not maintained up to 12 months because of the development of resistance mutations in reverse transcriptase of the *pol* gene of HIV (Larder *et al*. 1989; St. Clair *et al*. 1991; Kellam *et al*. 1992). Surprisingly, CD4 T cells did not fall in the patients treated with ZDV and KRG compared to ZDV monotherapy. Thus, we investigated whether there is a delay in the development of mutations along with maintenance of CD4 T cells. Nine patients treated with ZDV and

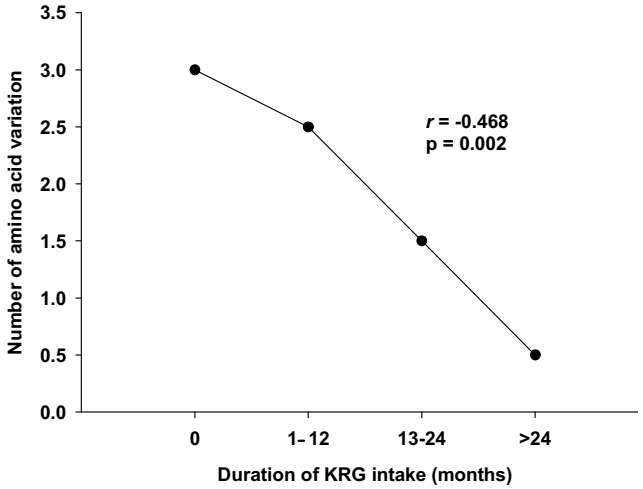

Fig. 3 Correlation between change of amino acid variation and duration of KRG intake. More than 2 clones for HIV-1 *env* C2/V3 region were determined in 44 patients. The number of amino acid variation between most similar 2 clones revealed an inverse correlation with the duration of KRG intake (Cho *et al*. 1997).

KRG maintained the CD4 T cell count steadily over 75 ± 24 months, whereas 9 patients with ZDV monotherapy revealed a significant decrease in CD4 T cells. In addition, the frequency of 6 resistance mutations (M41L, D67N, K70R, L210W, T215Y/F, and K219Q) was 21.7% in the former group and 56.3% in the latter group ($p < 0.01$). Interestingly, the frequency of the first resistance mutation, K70R was significantly higher in the former than that in the latter because second mutation, T215Y/F was nearly not developed in the former (Cho *et al*. 2001). Interestingly, we could not find multinucleoside drug resistance (MDR) mutations in our cohort treated with KRG (Cho *et al*. 1996, 2002) although the frequency of Q151M and related mutations has been reported to be 3.5 to >19% for patients treated with multiple nucleoside reverse transcriptase inhibitors for > 1 year (Kavlick *et al*. 1998; Maeda *et al*. 1998).

KRG slows depletion of CD4 T cell irrespective of HLA class I

We previously showed that long-term intake of KRG delayed disease progression in HIV-1-infected patients. To investigate whether this slow progression was affected by KRG-intake alone or in combination with HLA factor, we analyzed clinical data in 68 HIV-1-infected patients who lived for more than 5 years without antiretroviral therapy (Sung *et al*. 2005). The average KRG-intake over 112 ± 31 months was 4082 ± 3928 g, and an annual decrease in CD4 T cells was 35.0 ± 29/μL. Data analysis showed that there are significant inverse correlations between the HLA prognostic score and annual decrease in CD4 T cells ($r = -0.347$) ($p < 0.01$) as well as between the amount of KRG-intake and annual decrease in CD4 T cells ($r = -0.379$) ($p < 0.01$). In conclusion, these data show that KRG intake independently and significantly affected the slow depletion of CD4 T cells, irrespective of HLA class I (Sung *et al*. 2005).

Moreover, when we focused the same analysis method on the 31 patients who have been living for more than 10 years without any antiretroviral therapy, the effect of KRG intake was more prominent (Cho *et al*. 2004). Even in this small size study, we could observe significant correlations among the amount of KRG intake, the annual decrease in CD4 T cells (AD)($r = -0.53$, $p<0.01$), and plasma HIV-1 RNA copy ($r = -0.35$) ($p < 0.05$), whereas there was no significant correlation between HLA score and, AD or HIV-1 RNA copy number (Cho *et al*. 2004). The changes in CD4 T cell count in 2 groups with high intake (n = 16) and low intake (n = 15) of KRG was compared. The amount of KRG in both groups was 8478 ± 4197g and 870 ± 1007 g for 137 ± 15 months and 125 ± 16 months, respectively. The CD4 + T cell counts in groups with high and low intake decreased from 497 ± 154/μl to 340 ± 164/μl and from 663 ± 269/μl to 161 ± 145/μl, respectively. This corresponds to an annual decrease of CD4 T cells of 14 ± 9/μl and 49 ± 30/μl, respectively (Cho *et al*. 2004).

KRG intake attenuates the *nef* gene

Based on previous data, we have become interested in whether KRG therapy could affect HIV-1 genes in long-term slow progressors or long-term nonprogressors (LTNP) treated with KRG for a prolonged period. A small percentage of patients infected with HIV-1 remain symptom-free for more than 10 years in the absence of antiretroviral therapy. Of these, very few maintain a CD4 T cell count greater than 500/μl. These patients are referred to as LTNP. (Kirchhoff *et al*. 1995; Rhodes *et al*. 2000) Among LTNP, the presences of gross deletions in the *nef* gene (hereafter described as gΔnef) have been rarely reported (Deacon *et al*. 1995; Dean *et al*. 1996; Mariani 1996; Learmont *et al*. 1999). LTSP was defined as the annual decrease in CD4 T cells < 20/μl over 10 years in the absence of antiretroviral therapy. We found that there is an association between the duration of KRG intake and the occurrence of gΔnef ($p < 0.01$) (Cho *et al*. 2006). The detection of gΔnef was significantly inhibited by HAART (Cho *et al*. 2009). Recently, we found that the median time for first detection of g*Δnef* was 13 months (Cho *et al*. 2010). In conclusion, our data show that g*Δnef* is inducible by KRG intake and its proportion is dependent on the duration of KRG intake and dose. This response is a noble concept in AIDS therapy because there is no report that any antiretroviral drug induces deletion in the HIV-1 genes.

Effect on 5′LTR and gag region

Now, to investigate the relationship whether there are genetic defects in other genes of HIV-1 besides the *nef* gene, we determined the full sequences of HIV-1 in the 10 LTSP. Five out of the 10 were included in a pilot study consisting of a KRG-only group (n = 23) in 1991 (Cho *et al*. 1994). In addition to beneficial clinical findings, we obtained several important genetic defects in HIV-1. As a novel finding, we obtained significantly frequent gross deletion in the 5′LTR and *gag* region irrespective of the HIV-1 subtype (Cho *et al*. 2008, 2009). In addition, there were many premature stop codons or gross deletions in the *pol* gene in 7 (unpublished data) out of the same 10 patients who revealed g*Δnef* (Cho *et al*. 2010). These findings suggest that frequent genetic defects might be related to slow progression by long-term therapy of KRG.

Beneficial effects of a combination of KRG and HAART

To determine whether KRG has beneficial effects on HIV-1-infected patients administered HAART, we analyzed the CD4 T cell count, viral load, and resistance mutations to HAART in 46 individuals. The study population was divided into two groups, specifically, a combination of HAART plus KRG (n = 23) and HAART alone (n = 23). The annual increase in CD4 T cell count in the combination group was significantly higher than that in the HAART alone group ($p < 0.05$). High-level resistance mutations were significantly lower in the combination group than those in HAART alone (Sung *et al*. 2009).

FUTURE PERSPECTIVES

We think that our clinical trial with KRG is the longest follow-up study in the literature although there were several interruptions. Almost all patients revealed significant genetic defects in HIV-1. We anticipate that a patient who was diagnosed in 1988 can survive 30 years in the absence of

HAART. KRG is an herb of choice in patients in early stage, not indicated for HAART. KRG can be a good alternative in patients intolerable for HAART. Combination therapy such as HAART plus immune therapy like KRG could be considered as best regimen in the future. Further well designed studies are needed whether what is the most effective component and how long the potency of HAART plus KRG is maintained.

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