J Ginseng Res xxx (2017) 1–5

Contents lists available at ScienceDirect

Journal of Ginseng Research

journal homepage: http://www.ginsengres.org

Research article

Effect of Korean Red Ginseng intake on the survival duration of human immunodeficiency virus type 1 patients

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ARTICLE INFO

Article history:
Received 25 August 2016
Received in Revised form
21 November 2016
Accepted 8 December 2016
Available online xxx

Keywords:
annual decrease of CD4$^+$ T cells
human immunodeficiency virus/AIDS
Korean Red Ginseng
survival duration

ABSTRACT

Background: Long-term ginseng intake can increase longevity in healthy individuals. Here, we examined if long-term treatment with *Panax ginseng* Meyer (Korean Red Ginseng, KRG) can also enhance survival duration (SD) in patients with human immunodeficiency virus type 1 (HIV-1) infection.

Methods: We retrospectively analyzed 252 HIV-1 patients diagnosed from 1986 to 2013 prior to the initiation of antiretroviral therapy. Overall, 162 patients were treated with KRG (3,947 ± 4,943 g) for 86 ± 63 mo. The effects of KRG on SD were analyzed according to the KRG intake level and the length of the follow-up period.

Results: There were significant correlations between the total amount of KRG and SD in the KRG intake group ($r = 0.64$, $p < 0.0001$) as well as between total amount of KRG and mean annual decrease in CD4$^+$ T-cell count in all 252 patients ($r = -0.17$, $p < 0.01$). The annual decrease in CD4$^+$ T-cell count (change in cells/μL) was significantly slower in KRG-treated patients than in patients receiving no KRG (48 ± 40 vs. 106 ± 162; $p < 0.001$). The SD (in months) was also significantly longer in the KRG group than in the no-KRG group (101 ± 64 vs. 59 ± 40, $p < 0.01$).

Conclusion: KRG prolongs survival in HIV-1 patients, possibly by slowing the decrease in CD4$^+$ T-cell count.

1. Introduction

Progressive loss of CD4$^+$ T cells is the hallmark of human immunodeficiency virus (HIV) infection, and is accompanied by chronic inflammation and chronic immune hyperactivation [1]. In HIV patients, CD4$^+$ T cells gradually and persistently decrease from the normal level of 800−1,200/μL to 0/μL. Untreated patients die, on average, 11 yr after primary infection [2], but the introduction of highly active antiretroviral therapy (HAART) in 1996 has markedly reduced the rates of mortality and morbidity [3]. It is currently recommended that individuals infected with human immunodeficiency virus type 1 (HIV-1) be initiated on a combination of at least three antiretroviral agents, even in the early symptomatic stages [4]. However, persistent HIV-1 replication maintains the tissue reservoir during therapy [5], and long-term HAART causes many side effects and ultimately results in drug resistance with ensuing therapeutic failure [6]. Thus, alternative and adjuvant therapies may be needed as these patients age.

Several host and viral factors are known to affect the rate of disease progression [7,8]. For instance, polymorphisms in the human leukocyte antigen (HLA) and C−C chemokine receptor type 5 (CCR5) are important host variables that affect disease progression [9]. However, the 32-bp deletion in the *CCR5* gene (CCR5-Δ32) that is known to protect against infection has not been found in the Korean population [10]. However, we have shown significant inverse correlations between the HLA prognostic score and the annual decrease in CD4$^+$ T cells (AD) [11], as well as between Korean Red Ginseng (KRG) intake and RNA copy number [12]. Thus, KRG may slow disease progression in vulnerable populations.

Panax ginseng Meyer has long been used as a general tonic for promoting longevity in the Far East, especially in China, Korea, and Japan [13]. *P. ginseng* is well known as an adaptogenic agent that increases physical performance, vitality, resistance to stress, and immunomodulatory activity [14–17]. *P. ginseng* contains a series of ginsenosides, acid polysaccharides, and many trace elements [13]. Recently, the anti-inflammatory efficacy of ginseng and adjuvant

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http://dx.doi.org/10.1016/j.jgr.2016.12.006
p1226-8453 e2093-4947/$ – see front matter

Please cite this article in press as: Cho Y-K, Kim J-E, Effect of Korean Red Ginseng intake on the survival duration of human immunodeficiency virus type 1 patients, Journal of Ginseng Research (2017), http://dx.doi.org/10.1016/j.jgr.2016.12.006

activities of saponins have been demonstrated in animal models of inflammatory disease [18–21]. We are conducting a long-term series of studies on KRG, either alone or in combination with zidovudine or HAART, for the treatment of HIV-1 infection [10,11,22–28], and have documented significant benefits.

It is well known that the long-term intake of ginseng promotes longevity, as described in books on traditional medicine [13]. However, no previous report has described the long-term outcomes in a cohort treated with ginseng for a specific disease such as AIDS. Therefore, our ginseng AIDS cohort may be a good model to evaluate the historical hypotheses regarding the benefits of ginseng.

In our present study, we retrospectively analyzed the AD and survival duration (SD) of an AIDS cohort to determine whether KRG treatment improves the immune function and longevity of HIV-1 patients. Furthermore, this study was limited to the period prior to the initiation of HAART for each patient. Our data indicate that long-term treatment with KRG increases longevity in HIV-1 patients.

2. Materials and methods

2.1. Study population

This study included 252 HIV-1 patients whose $CD4^+$ T-cell counts were available prior to HAART. Of these, 207 were diagnosed during 1986–1992, 19 in 1993, and 26 during 1994–2013. First, we divided the patients according to the monthly amount of KRG (mKRG) intake (0 g, $\leq$ 30 g, or $>$ 30 g) and follow-up period ($<$ 10 yr, $n = 192$, or $>$ 10 yr, $n = 60$). This study was approved by the Institutional Review Board of Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

2.2. Treatment with KRG

Since November 1991, we have studied the effects of oral KRG (5.4 g/d; Korea Ginseng Corporation, Seoul, Korea) on patients with HIV-1 infection. We instructed patients to orally take six capsules (300 mg/capsule) three times daily [10,24]. There were several interruptions in KRG intake before 2001. The total amount of KRG (tKRG) supplied and yearly KRG intake in the 162 KRG-treated patients enrolled were 3,917 ± 4,972 g and 559 ± 435 g, respectively, over an interval of 86 ± 63 mo (Table 1).

Table 1
Effects of Korean Red Ginseng on $CD4^+$ cell count and SD of HIV-1 patients

Item	Group		*p*
	Non-KRG patients	KRG patients	
No. of patients	90	162	
Male:female	86:4	142:21	
Age (yr)	32.5 ± 9.2	30.3 ± 9.6	>0.05
No. of dead patients	30	52	>0.05
Suicide	4	2	>0.05
KRG supplied (g)	0	3,947 ± 4,943	
Range (g)	0	30–25,602	
Yearly KRG (g)[1)]	0	575 ± 474	
Baseline $CD4^+$ T cells (/μL)	539 ± 301	508 ± 239	>0.05
Last $CD4^+$ T cells (/μL)	302 ± 244	232 ± 223	<0.05
Interval (mo)	40 ± 32	85 ± 63	<0.001
AD (/μL)	106 ± 162	48 ± 40	<0.001
SD (mo)	59 ± 40	101 ± 64	<0.001
Survivor for >10 yr	8	52	<0.001
Survivor for >15 yr	1	14	<0.05

AD, annual decrease of $CD4^+$ T cells; HIV-1, human immunodeficiency virus type 1; KRG, Korean Red Ginseng; SD, survival duration

[1)] For the interval between the baseline $CD4^+$ T-cell count and the last $CD4^+$ T-cell count

2.3. $CD4^+$ and $CD8^+$ T-cell measurements

After staining peripheral blood mononuclear cells with phycoerythrin- and fluorescein isothiocyanate-conjugated antibodies raised against the CD4 and CD8 antigens (Simultest reagent; Becton Dickinson, San Jose, CA, USA), $CD4^+$ and $CD8^+$ T cells were counted using a FACScan flow cytometer (Becton Dickinson) at 6-mo intervals [9,22,23].

2.4. Definitions of $CD4^+$ T-cell count interval and SD

The $CD4^+$ T-cell count interval was defined from the first to the last $CD4^+$ T-cell measurement prior to HAART. SD (or follow-up period) was defined as the period between the diagnosis of HIV-1 infection and the last $CD4^+$ T-cell count measurement prior to HAART. Oral KRG was initiated after the first $CD4^+$ T-cell measurement. Hence, the duration of KRG intake was shorter than the defined $CD4^+$ T-cell count interval.

2.5. Statistical analysis

All data were expressed as mean ± standard deviation. Differences in categorical data were tested using the Chi-square test for paired groups or Fisher's exact test for multiple (3) groups. Correlation strength between the amount of KRG, and both SD and AD was tested by Pearson's coefficients. All statistical analyses were performed using SPSS package version 12.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. KRG slows $CD4^+$ T-cell count reduction and prolongs survival of HIV-1 patients

The 252 study patients consisted of 162 KRG-treated and 90 untreated (non-KRG) patients. There were no differences in the mean age, mortality, or suicide rate between groups. Furthermore, baseline $CD4^+$ T-cell count did not differ (Table 1). However, the yearly rate of $CD4^+$ T-cell decrease (AD) was significantly slower in patients of the KRG group than in those of the non-KRG group ($p < 0.001$; Table 1). Consistent with the slower fall in $CD4^+$ T-cell count, SD was also significantly longer in the KRG group. We found no significant difference in AD (in μL) and SD (in months) between patients receiving a lower monthly dose of KRG ($\leq$ 30 g, 15.5 ± 8 g/mo) and those receiving a higher dose ($>$ 30 g, 68 ± 32 g/mo) (AD: 57 ± 70 vs. 43 ± 79, SD: 94 ± 48 vs. 106 ± 73). There was, however, a significant difference in SD between the groups receiving 0 g (106 ± 163/μL in AD and 59 ± 40 mo) and $\leq$ 30 g of KRG (54 ± 69/μL in AD and 94 ± 48 mo). The proportions of survivors beyond 10 yr and 15 yr were significantly higher among the KRG-treated patients ($p < 0.01$; Table 1).

We also analyzed the effects of KRG intake and follow-up period on SD among the 252 study patients. We first divided the patients according to the mKRG intake (0 g, $\leq$ 30 g, or $>$ 30 g). The AD rates in mKRG $\leq$ 30 g and mKRG $>$ 30 g groups were significantly slower than those in the non-KRG (0 g) group ($p < 0.05$ and $p < 0.01$, respectively; Fig. 1A). Hence, SD was significantly prolonged in patients receiving any dose of KRG ($p < 0.001$, Fig. 1B). Compared with the non-KRG group, SD was significantly higher in the mKRG $\leq$ 30 g and mKRG $>$ 30 g groups.

3.2. Effect of KRG on AD

The cumulative dose depends on the total follow-up period; therefore, we also divided patients into two groups according to

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