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Research article

Korean Red Ginseng exhibits no significant adverse effect on disease activity in patients with rheumatoid arthritis: a randomized, double-blind, crossover study

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ABSTRACT

Background: *Panax ginseng* is a well-known immune modulator, and there is concern that its immune-enhancing effects may negatively affect patients with rheumatoid arthritis (RA) by worsening symptoms or increasing the risk of adverse effects from other drugs. In this randomized, crossover clinical trial, we evaluated the impact of Korean Red Ginseng (KRG) on disease activity and safety in RA patients.
Methods: A total of 80 female RA patients were randomly assigned to either the KRG (2 g/d, $n = 40$) treatment or placebo ($n = 40$) groups for 8 wk, followed by crossover to the other treatment group for an additional 8 wk. The primary outcome was the disease flare rate, defined as worsening disease activity according to the disease activity score 28 joints-erythrocyte sedimentation rate (DAS28-ESR). The secondary outcomes were development of adverse events (AEs) and patient reported outcomes. Outcomes were evaluated at baseline and 8 wk and 16 wk. The outcomes were compared using the Chi-square test.
Results: Of the 80 patients, 70 completed the full study. Their mean age was 51.9 yr, and most exhibited low disease activity (mean DAS28-ESR 3.5 ± 1.0) at enrollment. After intervention, the flare rate was 3.7% in each group. During KRG treatment, 10 AEs were reported, while five AEs were developed with placebo; however, this difference was not statistically significant ($p = 0.16$). Gastrointestinal- and nervous system-related symptoms were frequent in the KRG group.
Conclusion: KRG is not significantly associated with either disease flare rate or the rate of AE development in RA patients.

1. Introduction

Rheumatoid arthritis (RA) is a common chronic autoimmune disease with a worldwide prevalence rate of 0.5–1% [1]. It can be a debilitating and painful condition that affects multiple joints in individual patients and can lead to substantial loss of function and mobility [2]. The ultimate goal of RA treatment is to reduce pain by controlling inflammation, to prevent or delay joint damage, and to enhance patient quality of life [2,3]. Some patients report that conventional RA medicine often fails to improve health, does not reliably alleviate pain, and can produce undesirable side effects [4]. Therefore, many RA patients have pursued complementary and alternative medicine (CAM) as part of their treatment [5]. CAM has become increasingly popular for RA patients, with an estimated 18–94% reporting some level of CAM use throughout the world, across different geographic and ethnic groups, and among people of different social and economic backgrounds [6,7]. Previous reports have shown that a near-majority of Korean RA patients have had experiences with CAM use, and among patients who had never used CAM before their RA diagnosis, roughly 11% used CAM within 1 yr [8].

Panax ginseng Meyer is a herb that has been used as a component of CAM for hundreds of years in Korean traditional medicine [9]. The principal active components of *P. ginseng* are the ginsenosides (or triterpenoid saponins) of ginseng, as well as approximately 38 additional types of ginsenosides that have been identified [10]. Prior experimental work suggests that ginseng's antiinflammatory effect could provide a feasible way to treat RA symptoms [11,12]; for example, by regulating tumor necrosis factor expression or Th17 cell

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activity [13,14]. A significant concern, however, is that ginseng treatment could exacerbate this autoimmune disorder because it leads to immune enhancement. Furthermore, few health practitioners recommend additional health food supplements for acute patients that are prescribed a broad range of drugs, because this might increase the risk of adverse events (AEs) [7]. However up to now, there has been no evidence of an interaction between RA treatment and Korean Red Ginseng (KRG), and there has been no randomized clinical trial examining the effect of *P. ginseng* on RA patients. The aim of the present study was to evaluate the impact of KRG on disease activity and safety in RA patients.

2. Methods

2.1. Study population

Patients with RA were screened according to the inclusion and exclusion criteria and enrolled prospectively between March 2015 and September 2015. Inclusion criteria were as follows: (1) female RA patients between the ages of 19 and 80 yr who satisfied either the 1987 American College of Rheumatology criteria or 2010 American College of Rheumatology/European League Against Rheumatism criteria; and (2) low disease activity [i.e., score less than 3.2 on the Disease Activity Score (DAS) 28-joint-erythrocyte sedimentation rate (ESR), DAS 28-ESR]. Exclusion criteria were as follows: (1) pregnant or breast-feeding; (2) any laboratory test abnormality; (3) use of ginseng extract within the last 2 mo; (4) known allergy to ginseng extract; (5) regular use of corticosteroids; and (6) moderate or high disease activity ($\geq$ 3.2 on the DAS28-ESR).

All patients provided informed consent. This study was approved by the Institutional Review Board of Hanyang University Hospital (HYUH 2015-01-001). The study protocol was registered with the Clinical Research Information Service of the Republic of Korea (KCT0001516).

2.2. Study design

We undertook a crossover trial to allow each patient to serve as his or her own control. A total sample size of 69 provided a power of 0.8 to detect noninferiority using a one-sided t test when the relative margin of equivalence was 0.3 and the significance level was 0.05. We utilized a crossover design with an equal number of patients in each sequence. However, considering a withdrawal rate of 14–15%, we required 40 patients in each arm. Sample size was calculated using PASS 2008.

Patients were randomized to receive either 8 wk of treatment with KRG (Period 1) followed by 8 wk of placebo (Period 2) or 8 wk of placebo (Period 1) followed by 8 wk of treatment with KRG (Period 2). Treatment doses were 2 g of KRG using 500 mg tablets, which were manufactured by the Korea Ginseng Corporation (Seoul, Korea) and were composed of ginsenoside Rg1 + Rb1 + Rg3 > 5.5 mg/g and cellulose. Placebo tablets, identical in size, weight, color, and taste, were also provided from Korea Ginseng Corporation (Figure 1). The use of nonsteroidal antiinflammatory drugs or disease-modifying antirheumatic drugs for controlling the RA disease activity was not restricted during the study period. Randomization was performed by a third party using a computer-generated random sequence. Study investigators, participants, and their caregivers were blinded by ensuring both KRG and placebo medication was delivered in identical capsules and boxes, with neither the investigator providing the medication nor the participants being aware of the allocated treatment. All randomized participants underwent baseline assessment consisting of a physical examination, history, and laboratory testing. Outcomes were measured at baseline and wk 8 and 16.

2.3. Outcome measures

2.3.1. Primary outcome

2.3.1.1. RA flare as defined by DAS28. The primary outcome measure was the flare rate during the KRG period compared with the flare rate during the placebo period. The disease flare was defined as an increase of more than 1.2 in the DAS 28-joint count ESR compared to baseline. The DAS28 is widely used to quantify disease activity and therapeutic response for RA patients. The DAS28 is a complicated formula with several disease elements as follows: $\text{DAS28} = 0.56 \times \sqrt{(\text{tender28})} + 0.28 \times \sqrt{(\text{swollen28})} + 0.70 \times \ln(\text{ESR}) + 0.014 \times$ patient global health visual analogue scale (VAS) [15].

2.3.2. Secondary outcome

2.3.2.1. AEs. Safety was assessed based on the type and severity of AEs. AEs were classified using the System Organ Class of the Medical Dictionary for Regulatory Activities (MedDRA version 11.1).

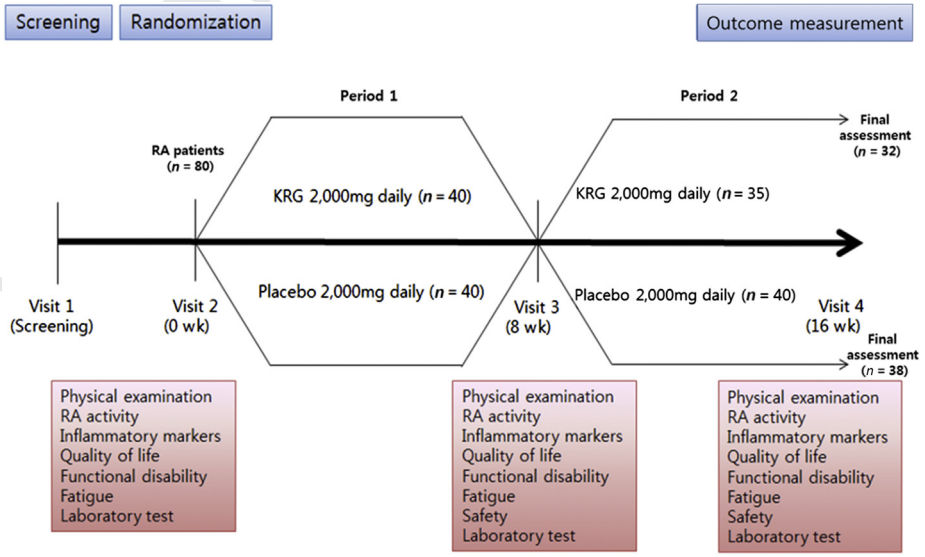

Fig. 1. Study design.

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