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File: ■ Korean Red Ginseng (*Panax ginseng*, Araliaceae)
■ Rheumatoid Arthritis
■ Safety

HC 061831-595

Date: June 30, 2018

RE: Korean Red Ginseng Does Not Increase Disease Flare Rate or Adverse Events in Patients with Rheumatoid Arthritis

Cho SK, Kim D, Yoo D, Jang EJ, Jun JB, Sung YK. Korean red ginseng exhibits no significant adverse effect on disease activity in patients with rheumatoid arthritis: a randomized, double-blind, crossover study. *J Ginseng Res*. 2018;42(2):144-148. doi: 10.1016/j.jgr.2017.01.006.

Rheumatoid arthritis (RA), a chronic autoimmune disease, can lead to loss of joint function and mobility. Treatment for the disease aims to control inflammation, reduce pain, prevent or delay joint damage, and enhance quality of life. Some patients report that because conventional medicine does not adequately reduce symptoms or causes intolerable side effects, they use complementary and alternative medicine to treat RA. In Korean traditional medicine, Korean red ginseng (KRG, *Panax ginseng*, Araliaceae) has been used for hundreds of years. The authors conducted a randomized, double-blind, crossover study to examine the effects of KRG on RA disease activity and to evaluate potential adverse effects in patients with RA.

Female patients with RA were screened from March 2015 to September 2015 for the following inclusion criteria: age between 19 and 80 years; RA diagnosis based on the 1987 American College of Rheumatology criteria or the 2010 American College of Rheumatology/European League Against Rheumatism criteria; and low disease activity, as indicated on the Disease Activity Score 28-erythrocyte sedimentation rate (DAS 28-ESR) calculator for RA. Exclusion criteria included pregnancy/lactation, lab abnormalities, prior use or allergy to ginseng extract, and use of corticosteroids.

The study was conducted in two phases. Forty patients were randomized to KRG treatment during phase 1 and placebo during phase 2. Another forty patients were randomly assigned to placebo during phase 1 and KRG treatment during phase 2. Each phase lasted 8 weeks. A washout period was not used between phases.

KRG 500 mg tablets were used (Korea Ginseng Corporation; Seoul, Korea). The tablets included ginsenosides Rg 1 + Rb1 + Rg3 > 5.5 mg/g and cellulose. The daily KRG dose was 2,000 mg. Placebo tablets (not described) were also provided by the Korea Ginseng

Corporation and were identical to the KRG tablets in size, weight, color, and taste. Patients were allowed to use nonsteroidal anti-inflammatory drugs and disease-modifying antirheumatic drugs throughout the study.

The primary outcome was RA flare rate (as defined as increases of more than 1.2 on the DAS 28-ESR compared with baseline) which as assessed at weeks 8 and 16. The DAS 28 is used to measure disease activity and treatment response in patients with RA. Safety was assessed by evaluating the type and severity of reported adverse effects (AEs). Other measures included changes from baseline in clinical laboratory parameters, changes in fatigue as indicated on a visual analogue scale (VAS) and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale, which includes 13 questions scored from 0 to 4.

Functional disability was assessed with a 20-item health assessment questionnaire-disability index. Its eight components (standing up, walking, dressing, hygiene, eating, reaching, gripping, and performing specific activities) were scored from 0 (without any difficulty) to 3 (unable to complete the task). The EuroQol questionnaire was used to rank mobility, self-care, usual activities, pain/discomfort, and anxiety/depression from 1 (no difficulty) to 3 (extreme difficulty).

The patients were aged 51.9 ± 9.35 years and had lived with RA for 7.8 ± 5.4 years on average. Most patients had a low disease activity (mean DAS 28-ESR of 3.5 ± 1.0). Ten (12.5%) patients had been prescribed glucocorticoid drugs to take as needed. Of the 80 patients who began the study, five patients withdrew during the first phase (one because of nausea, one because of arthritis worsening, and three due to withdrawal of consent). During the second phase, five patients withdrew from the study (one because of uterine surgery, one who had an abnormal liver function test, one because of a fracture, one who complained of headache, and one due to withdrawal of consent).

Using an intent-to-treat analysis, the authors compared the RA flare rate during KRG treatment with that during placebo treatment and found identical flare rates—3.7% in both groups. Using a per protocol analysis,there was no significant difference in the change in disease activity between the groups (P = 0.77).

Fatigue VAS improved more, during the KRG phase compared with the placebo phase, but this was not significant (P = 0.57). Improvement in fatigue measured on the FACIT-F scale was also greater in the KRG phase compared with the placebo phase, but this also was not significant (P = 0.25). "This lack of statistical significance might be due to an inadequate sample size, or it is possible that the participant group had an insufficient number of baseline fatigue scores to observe a statistical improvement after KRG treatment," the authors write. Improvements in functional disability (P = 0.74) and quality of life (P = 0.78) were greater during the KRG phase compared with the placebo phase, but the differences were not statistically significant.

AEs totaled 10 during the KRG phase and 5 during the placebo phase. There was no statistically significant difference in the rate of adverse events between groups (P = 0.16). The most frequently reported AEs during KRG treatment were gastrointestinal disorders (n = 5) and nervous system disorders (n = 3). Three treatment-emergent AEs were reported with each group. In the placebo group, a hepatobiliary disorder occurred in one patient and gastrointestinal disorders in two patients. In the KRG group, the

treatment-emergent AEs included gastrointestinal disorders in two patients and a nervous system disorder in one patient.

Among the study's limitations are the lack of a washout period and the short treatment period. Because the study included only patients with low disease activity who were not taking corticosteroids, generalizing the results for all patients with RA would be difficult.

The authors conclude that "KRG is not significantly associated with either disease flare rate or the rate of AE development in RA patients."

—Shari Henson

Referenced article can be accessed at
https://www.sciencedirect.com/science/article/pii/S1226845316302159.