American Ginseng for the Treatment of HIV Fatigue: A Randomized Clinical Trial

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Background

- HIV-associated fatigue is a prevalent and debilitating symptom linked to neurocognitive deficits, nonadherence, and poor quality of life (QOL) and physical functioning.
- The etiology of fatigue in HIV infection is multifactorial
- Management of HIV fatigue is based on the treatment of cause-specific conditions or treating the symptom of fatigue directly.
- However, the use of available therapies are limited by their unclear effectiveness, adverse events, costs, and potential for abuse.
- Patients may use complementary and alternative medicines to treat fatigue, but the safety and efficacy of these approaches have not been studied.
- Animal and human studies have demonstrated that ginseng may improve fatigue symptoms.
- A placebo controlled clinical trial with American ginseng (AG) at doses of 750-2000 mg/day for 8 weeks, showed positive trends for improvement of cancer-associated fatigue.
- We conducted a randomized placebo controlled trial with standardized AG 1000 and 3000 mg daily to determine the effects of this dietary supplement on fatigue in HIV-infected adults.

Objectives

- To determine whether encapsulated standardized AG powdered root 1000 and 3000 mg PO QD for 28 days ameliorates HIV fatigue compared to matching placebo.
- To evaluate the safety and tolerability of encapsulated standardized AG powdered root 1000 and 3000 mg PO QD for 28 days in HIV-infected adult subjects with fatigue.

Methods

Study Participants Selected Inclusion Criteria

- HIV-infected adults on ART for ≥3 months
- Undetectable HIV RNA
- Fatigue Severity Score (FSS) ≥ 4.5
- Without other illnesses associated with fatigue, such as renal disease, anemia, hypothyroidism, untreated hypogonadism, depression or insomnia

Study Design

- 6-wk double-blinded randomized, parallel-arm placebo-controlled trial
- Compared encapsulated standardized AG (≥5% total ginsenosides) 1000 and 3000 mg powdered root PO QD for 28 days to placebo
- Patient Reported Outcomes (PROs): FSS, Insomnia Severity Index (ISI), Patient Health Questionnaire (PHQ)-9, Brief Fatigue Inventory (BFI), Epworth Sleepiness Scale (ESS), Medical Outcomes Study HIV Health Survey (MOS-HIV), Clinical Global Impressions (CGI), and PROMIS Fatigue were assessed at enrollment and weeks 2-6.
- Adherence was monitored by self-report/pill count.
- Safety laboratory tests were obtained at every visit.

Outcomes Measures

- Primary endpoint: average change in FSS from baseline to week 4.
- Secondary endpoints: other measures of fatigue and safety/tolerability from baseline to week 4:
  - Sleep quality, depression, and QOL: BFI, ESS, PHQ-9, ISI, MOS-HIV, CGI, and PROMIS Fatigue.

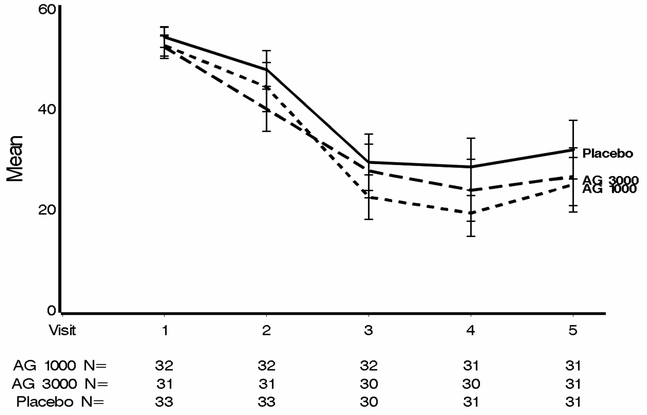
Data Analysis

- Changes were compared between the AG and placebo arms using nonparametric Wilcoxon tests supplemented with repeated measures mixed models to adjust for age, gender, race, baseline insomnia, and depression.
- Data was analyzed using an intent-to-treat approach.

Results

- 96/120 planned subjects were enrolled; 3 were lost to follow up (1 AG 1000mg and 2 Placebo) and 3 discontinued study agent prematurely (1 AG 3000mg and 2 Placebo).)
- 32 randomized to AG 1000mg, 31 to 3000mg, and 33 to placebo (Table 1)
- **FSS changes were not significantly different between the AG arms and placebo (Figure 1).**
- There was an overall improvement in the placebo and AG arms for all PROs (Table 2).
- PRO values conversion to 0-100 score scale also showed high proportion of participants who improved ≥10 points in the AG and placebo arms: FSS 72%, PHQ-9 59%; 63%; ISI 47%; PROMIS Fatigue 76%; BFI "improved right now"; ESS 75%; 73% MOS-HIV energy-fatigue .
- **However, there was no significant differences in improvements in the AG and placebo arms**
- **Post-hoc analysis combining the AG arms confirmed that fatigue was no different than placebo on FSS; AG showed modest improvements in fatigue on 3/4 BFI subscales (p=0.01-0.03) and trends toward improvement in 4/10 MOS HIV QOL subscales.**
- Overall mean adherence by pill count and self report was ≥96% for all study arms.
- Most adverse events were grades 1 and 2; all recovered and did not differ by study arms.
- Only 2/5 neutropenia severe adverse events were rated as possibly associated with study agent (1 AG 3000mg and 1 Placebo); all recovered.

Figure 1: Primary Endpoint: Change Mean FSS Over Time



There is trend for the mean FSS to be lower on the AG arms than placebo. However, there were not significant differences in FSS between placebo and either of the AG arms.

Table 1: Subject Characteristics at Baseline (N=96)

Variables	AG 1000 mg (N=32)	AG 3000 mg (N=31)	Placebo (N=33)	Total (N=96)
Age (y) Median (Q1, Q3)	53 (49, 57)	54 (50, 59)	51 (47,57)	52.5 (48, 57)
Sex, Female	14 (44%)	13 (42%)	17 (52%)	44 (46%)
Race, % Black	100%	81%	91%	91%)
CD4 Count (/mm³); Median (Q1, Q3)	622 (495.5, 703)	619 (338, 798)	651 (403, 751)	621.5 (410.5,743)

Table 2: Mean (SD) Decrease in PROs for AG and Placebo Arms from Baseline to Week 4

PROs	AG 1000 mg (N=32)	AG 3000 mg (N=31)	Placebo (N=33)	P-value
FSS	-24.7 (18.6)*	-16.9 (15) *	-18.7 (17.4) *	p=0.15 AG 1000mg vs placebo p=0.73 AG 3000mg vs placebo
PHQ-9	-5.5 (4.8) *	-2.9 (4.2) *	-4.8 (4.2) *	p=0.68 AG 1000mg vs placebo **p= 0.058** AG 3000mg vs placebo
ISI	-6.9 (6.1) *	-3.4 (5.5) *	-4.6 (5.2) *	p=0.17 AG 1000mg vs placebo p= 0.51 AG 3000mg vs placebo
PROMIS Fatigue	-12.5 (11.8) *	-11.4 (11) *	-10.4 (10.9) *	p=0.47 AG 1000mg vs placebo p=0.41 AG 3000mg vs placebo
BFI	-40 (31.3) *	-33.3 (30.6) *	-26.8 (32.7) *	p= 0.12 AG 1000mg vs placebo p= 0.59 AG 3000mg vs placebo
ESS	-5.7 (7.1) *	-7 (5.2) *	-6.2 (3.9) *	p=0.75 AG 1000mg vs placebo p= 0.74 AG 3000mg vs placebo
MOS	22.4 (20.9) *	24 (22.1) *	20.1 (20.2) *	p=0.79 AG 1000mg vs placebo p= 0.55 AG 3000mg vs placebo

***p<0.05 for within-group change**

Conclusions

- **Encapsulated standardized AG powdered root 1000 and 3000 mg/daily for 28 days did not reduce HIV-associated fatigue compared to placebo.**
- **Overall adherence was high and both doses of AG were well tolerated**
- **The clinical significance of the small improvements in the AG arms in some of the secondary endpoints relative to the large placebo effect is unclear.**
- **Conditional power analysis indicated that the likelihood of the observed significance changing with additional sampling was very small.**

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