SAFETY AND EFFICACY OF CKBM-A01, A CHINESE HERBAL MEDICINE, AMONG ASYMPTOMATIC HIV PATIENTS

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Abstract. Complementary remedies represent a potential alternative treatment for chronic diseases, including HIV/AIDS cases not meeting criteria for using highly active antiretroviral therapy (HAART). This study evaluated the safety and efficacy of CKBM-A01, a Chinese herbal medicine, and patient quality of life (QoL). Asymptomatic HIV patients with CD4 counts of 250-350 cells/μl were recruited into this open-labeled trial. Liquid CKBM-A01 was prescribed for a 36-week period. Study participants recorded all symptoms themselves on diary cards. Study parameters, including CD4 cell counts, HIV viral loads, and blood chemistry, were periodically monitored and questionnaires were used to assess QoL and to help with risk reduction. Eighteen volunteers, mean age (± SD) 32.07 (±6.88) years, had a median (interquartile range, IQR) baseline CD4 count of 292 (268.50-338.25) cells/μl. No serious drug-related adverse events due to CKBM-A01 were detected during the study. Intermittent diarrhea was reported in 55.6%, weakness or skin rash/itching in 50%, and increased bowel movement in 33.7%. No significant changes in log viral load or CD4 cell counts were observed at the end of the study. Most of the volunteers (72.2%) expressed satisfaction with CKBM-A01 and had a positive perception. Common colds and nasal symptoms were significantly lower during treatment (p=0.019). CKBM-A01 appeared to be safe but gave no significant improvement in QoL in asymptomatic HIV patients, and gave no significant improvement in the treatment of HIV based on CD4 cell counts and viral loads.

INTRODUCTION

The current guidelines for initiating anti-retroviral therapy in HIV-infected patients are based on CD4 cell counts and plasma HIV RNA levels (Gazzard *et al*, 2006; Hammer *et al*, 2006; del Rio, 2008). Asymptomatic HIV-infected individuals not meeting criteria for highly active antiretroviral therapy (HAART) usually seek other options, including alternative medicines, and traditional herbs and remedies. Not surprisingly, most patients with incurable chronic diseases, such as malignancies, cerebrovascular diseases, and HIV/AIDS, prefer to take herbal medicines (Vickers *et al*, 1999; Wu *et al*, 2001). The growing interest in herbs is attributable not only to concerns about the high cost of western medicines, but also the rigor and undesired side-effects of conventional medical treatments (Ernst, 2000). Natural organic compositions in herbal medicines are felt by patients to be safer with

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fewer adverse effects.

Chinese herbal medicines have been used for centuries. CKBM-A01, a Chinese herbal medicine, is an oral liquid solution of herbal extracts and yeasts. Toxicological studies in animal models have indicated it to be safe and has promising immunogenic effects. The results of a pilot human study of CKBM-A01 among HIV/AIDS cases in Beijing, China, suggested the product was safe and efficacious in increasing CD4 cell counts (unpublished data). CKBM-A01 may be beneficial to HIV patients if it has the ability to maintain CD4 cell counts above 200 cells/μl, or slows the rate of CD4-cell decline. This clinical trial evaluated the safety and potential efficacy of CKBM-A01 immunoenhancing effects, and related quality of life, including morbidity, among asymptomatic HIV-infected patients.

MATERIALS AND METHODS

The herbal formula CKBM-A01 (CK Life Sciences International, China) has 2 major components, the crude herbs *Panax ginseng Mey* (Ginsenosides) 1.2% w/v and *Schisandrae chinensis Baill* (*wuweizu*) 2.3% w/v, combined with other fruits and natural products, including *Ziziphus jujube Mill* (jujube) 3.9% w/v, *Crataegus pinnatifida* Bge (hawthorn) 3.9% w/v, *Phaseolus radiatus* L (mung bean) 2.3% w/v, *Glycine Max* (soyabean) 6.9% w/v, *Saccharomyces cerevisiae* (baker's yeast) 0.1% w/v, apple 4.7% w/v, honey 1.7% w/v, and water. The dosage of CKBM-A01 was a 90-ml bottle twice daily for 36 weeks. The product was developed and produced by CK Life Sciences International, China, and its quality was assured and tested for toxicity and contamination by Healthcare and Pharmaceutical Services, SGS Hong Kong.

This prospective, open-label, phase II study was conducted during April 2006-March 2008, at the Clinical Infectious Diseases Research Unit, Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, in Bangkok. The study protocol was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, and the study followed good clinical practice guidelines. Screening was carried out among 54 asymptomatic HIV-infected Thais who gave written informed consent; 18 were eligible and enrolled into the study according to the inclusion criteria: asymptomatic HIV-infected individuals with CD4 cell counts of 250-350 cells/μl. The exclusion criteria were: history of allergy to any ingredient in CKBM-A01, an abnormal liver function test (> 3 times the normal range), complete blood count, renal function test, blood nitrogen, or electrolytes (> 1.5 times the normal range). Anyone with serious, uncontrolled opportunistic infections within 14 days of screening, or a history of concomitant investigational product use within 4 weeks of screening, or pregnancy or breastfeeding, was excluded. All female participants were required to agree to use effective contraception and had to have a negative pregnancy test before enrollment, and throughout the study period.

Safety and efficacy assessment

During the CKBM-A01 trial, the safety profile was assessed every visit, at weeks 4, 12, and 36, via history-taking, physical examination, laboratory investigation (CBC, liver function test, blood urea nitrogen, serum creatinine, electrolytes), and other appropriate tests, as required. Abnormal daily symptoms, such as feeling cold, fever, diarrhea, headache, or insomnia, were self-recorded on a diary card. Any urgent or severe adverse event was reported directly to the investigators, who were on 24-hour standby. Adherence to the study drug was self-assessed by diary card and rechecked by drug counts.

Apart from CD4 and viral load assessment at weeks 12, 24, and 36, immunological function *in vivo* was also measured through delayed-type hypersensitivity (DTH) to recall common antigens at baseline and at the end of the study. Intradermal injections of 0.1 ml (Mantoux method) of the following antigens were used for DTH testing: 1) tuberculin purified protein derivative (PPD) 10 IU/0.1 ml (Thai Red Cross, Bangkok, Thailand), 2) tetanus toxoid 10 lf/0.5 ml (Biogenetech, Barga, Italy) and 3) *Candida albicans* allergen extract 1:20 w/v (Greer Laboratories, Lenoir, USA) at a 1:500 dilution. The criterion for a positive DTH reaction was a detectable induration ≥5 mm at the antigen site (CDC, 1997).

Quality of life assessment

As another outcome, patient quality of life (QoL) was assessed, an important factor in chronic debilitating and morbid diseases, such as HIV/AIDS. Functional outcomes were significantly associated with HIV mortality, even after controlling for CD4 cell counts. The questionnaire used in this study was the Functional Assessment of Human Immunodeficiency Virus Infection, version 4 (FAHI), a 47-item generic QoL measurement instrument covering 5 domains: physical wellbeing, emotional wellbeing/living with HIV, functional and global wellbeing, social wellbeing, and cognitive function (Cella *et al*, 1996). FAHI, a psychometrically sound instrument that captures multiple important dimensions of HIV/AIDS-related QoL was performed at baseline, then at weeks 4, 12, 24, and 36. Education regarding risk reduction and counseling were conducted at each visit during the 36-week study. Positive perceptions and benefits were also evaluated at the end of the study.

For safety reasons, the withdrawal criteria for discontinuation of the study drug and switching to a standard anti-retroviral regimen, included disease progression (CD4 count <200 cells/μl, or the occurrence of AIDS-defining illness), and unacceptable adverse events (significant change from baseline on clinical and laboratory evaluation by the study physician). Data monitoring of rate of accrual, compliance, follow-up and AE incidence, was conducted regularly according to the relevant good clinical practice and regulatory guidelines.

Sample size calculation

Simon's Optimal Two-stage Design was used to calculate sample size, based on an assumed 30% response rate from the CKBM-A01 treatment group. A positive response was defined as an increase in CD4 cell count of 50 cells/μl or more above baseline at the 36-week evaluation, or during the last documented visit. The sample size was 18. If 3 or more positive responses occurred, the trial could have proceeded to recruit 17 more patients. With > 6 responses from the 35 patients, after 2 stages conducted, it could be concluded that CKBM-A01 was significantly effective.

Statistical analysis

Changes in CD4 cell counts and safety parameters from baseline were tested at each visit by Wilcoxon signed-rank test. Regarding QoL, morbidity rate, and viral load over the 36-week study, changes in values from baseline were tested by McNemar's chi-squared or Wilcoxon signed-rank test, as appropriate.

RESULTS

Background characteristics

All 18 HIV-infected patients, mean age (± SD) 32.07±6.88 years, were enrolled in the study. All the studied patients were naïve to antiretroviral treatment, with a median (Interquartile range, IQR) HIV time of 93.2 weeks (49.9-156.6) before enrollment in the study. Most of the patients (55.6%) were >30

years old, and 66.7% (12/18) were female. The majority were married (66.7%). One third of married patients had discordant HIV status from their partners, 1/3 had a concordant status, and the status of the partner was unknown in 1/3. All subjects reported contracting HIV through sex: heterosexual in 83.3%, homosexual in 11.1% and bisexual in 5.6%. Forty-one point six percent of females had one partner (monogamous) while the rest had multiple partners. Almost half (44.4%) were symptomatic or had a previous history of herpes zoster (stage B, CDC, 1993) while the others were asymptomatic (stage A, CDC, 1993). No underlying diseases or history of opportunistic infections were detected. No patient withdrew consent during the 12-month study. All adhered to the scheduled dosage of CKBM-A01 per protocol, for 9 months. Missing doses of no more than 3 sequential doses were reported in 7 of 18. The median (range) of total missed doses was 2 (1-8).

Safety profile

There were no severe adverse events (SAE) related to the investigational drug. However, 2 SAE were reported in 1 patient: dengue fever and cervical adenocarcinoma. The female subject experienced acute fever followed by voluminous vaginal bleeding for 11 days after 8 weeks of CKBM-A01 administration. Her final diagnosis was dengue hemorrhagic fever. One month later she developed menorrhagia with severe anemia which was diagnosed as cervical carcinoma in situ. She received standard treatment and decided to continue taking CKBM-A01 as scheduled until the end of the study.

Commonly reported symptoms included intermittent diarrhea (55.6%), weakness (50%), skin rash/itching (50%), headache (44.4%), myalgia (38.9%), increased bowel movements (33.7%), nausea (33.3%), abdominal pain (27.8%), anorexia (27.8%), confusion (27.8%), depression (27.8%), dizziness (22.2%), eosinophilia (16.7%), vomiting (11.1%), toothache (11.1%), backache (11.1%), dyspepsia (11.1%), arthralgia (11.1%), heartburn (11.1%), insomnia (5.6%), constipation (5.6%), dysmenorrhea (5.6%), urinary tract infection (5.6%), anemia (5.6%), somnolence (5.6%), blurred vision (5.6%), and edema (5.6%). The median (range) onset and duration of related adverse events was 1 day (range 1 day-18 weeks) and 1 week (range 1 day-8 weeks), respectively. The adverse events were well-tolerated and no study participant ceased taking the drug due to adverse events.

Other illnesses detected during the study included viral infection (61.1%), worsening rhinosinusitis (33.3%), urinary tract infection (5.6%), genital herpes simplex infection (11.1%), herpes zoster infection (11.1%), dengue fever (5.6%), opisthorchiasis (5.6%), intestinal amebiasis (5.6%), cervical adenocarcinoma (5.6%), and hemorrhoids (5.6%) during 1 year of evaluation. All symptoms had resolved by the end of the study. There were no significant changes in hemoglobin, white blood cell count, platelet count, liver enzyme levels, or creatinine levels during the 12-month study period (Table 1). During the study, 2 patients terminated at weeks 24 and 36 due to CD4 count drops to 154 (12%) and 172 (13%) cells/μl. The reason for early termination was to enable the patient to undergo antiretroviral therapy. The CD4 count in one patient increased to 221 (16%) after early termination.

Efficacy assessment

The 18 patients had a median (range) base-line CD_4 count of 292 (237-348) cells/ml. Two patients with CD_4 counts of 243/μl (23%) and 237/μl (17%) were enrolled in the study with sponsor agreement. This was done after clinical assessment by a study physician. The investigators agreed to ask the sponsor for protocol exemption before conducting the study procedures. The mean

Table 1
Safety parameters during the study.

Parameters median (IQR)	Baseline	Week 4	Week 12	Week 36	*p*-value
WBC(10^3/μl)	5.1 (4.5,6.1)	5.2 (4.7,5.6)	5.3 (4.4,5.8)	5.2 (4.3,6.0)	> 0.05
Hemoglobin (g/dl)	12.7 (11.6,14.6)	12.7 (11.9,14.1)	12.4 (11.7,14.8)	12.7 (12.1,14.2)	> 0.05
Platelet (/μl)	235.0 (201.2,293.0)	243.0 (187.0,282.5)	262.5 (190.2,311.5)	258.0 (186.5,281.2)	> 0.05
Creatinine (mg/dl)	0.65 (0.60,0.83)	0.65 (0.60,0.80)	0.70 (0.50,0.80)	0.65 (0.60,0.90)	> 0.05
AST (Unit/l)	19 (15.8,22.8)	18 (16.0,22.5)	18 (16.0,23.0)	21 (17.7,25.2)	> 0.05
ALT (Unit/l)	17 (15.0,25.5)	15.5 (13.0,21.8)	15 (11.8,28.8)	18 (11.0,25.5)	> 0.05
Na (mmol/l)	137 (135,138.25)	137 (135.0,138.2)	138 (135.8,139.0)	137 (135.8,139.0)	> 0.05

follow-up CD_4 counts in these 2 subjects at weeks 12, 24, and 36, were 267.5/μl, 268/μl, and 270/μl, respectively. There was no statistically significant change in the CD4 cell count between the start and month 9 of treatment (p=0.08). The median viral loads at the start of treatment and week 36 were 4.8log and 4.89log copies/μl, respectively. No significant changes in log viral load were observed by 36 weeks of treatment (p>0.05). Regarding the primary endpoint of the study, the trial was terminated after completion of stage I because only 2 patients at week 36 had CD4 counts which increased > 50 cells/μl (52, 128 cells/μl) from baseline.

Regarding DTH skin tests at baseline and 9 months post-treatment, all patients showed positive reaction to either tetanus or *Candida albicans* at baseline. Tetanus, *Candida albicans* and PPD skin tests were positive in 17/18, 7/18, and 4/18, respectively. By the end of treatment, there were no additional responses to other allergens.

Assessment of quality of life

Most patients reported improved physical status, such as reduced nausea, pain, fatigue, and coughing. However, there were no obvious changes in emotional well-being by week 36 of the study. The total QoL score was not statistically different at the end of the study from baseline (p = 0.813). There were also no significant changes in social, functional or cognitive wellbeing. However, 13 volunteers (72%) still perceived improved wellbeing due to satisfaction with treatment. Mean body mass indexes (BMI) at baseline and at the end of study were 21.9 and 20.8 kg/m^2, respectively (p>0.05). The frequency of common colds during the last 3 months of the study were reported to be significantly lower than the first 3 months of the study (p=0.019). When only cases of underlying chronic rhinosinusitis were considered, the number of cold and nasal symptoms decreased significantly after starting CKBM-A01 (p=0.02).

Counseling and risk reduction assessment

We provided education and counseling at each visit during the study and also evaluated sexual risk behavior at baseline and at the end of the study. Most patients indicated practicing safe sex with a single partner, or abstinence. Only 3/18 had multiple sex partners. At the end of the study, 100% condom use was reported by every subject, while baseline use was 83%. All patients reported benefiting from participation in the study through health education (77.8%) and improved healthy perceptions (55.6%).

DISCUSSION

HIV/AIDS remains a burden on the national economy and the public health bud-

get, with a peak distribution in the working-age group, as found in this study. The use of antiretroviral drugs has occupied the attention of government-funded health insurance and national health insurance systems for all Thai employees and citizens. However, some HIV-infected patients experience fear and barriers to access to treatment for many reasons, including social stigma, adverse rumors about drugs via the mass media, and the inconvenience of obtaining care at health centers and hospitals. The finding of unknown HIV status among 1/3 of the subject partners should raise concerns about HIV transmission among married couples or high risk individuals, due to a general lack of awareness of asymptomatic HIV infection in society. This issue should be stressed during counseling for HIV testing.

Herbal medicines and complementary treatments may be potential alternatives for HIV-infected individuals who do not meet criteria for antiretroviral therapy. Ginseng is used to boost the immune system and enhance stamina and physical capacity. In *in vitro* and *in vivo* studies of ginseng, one ingredient in CKBM-A01, immunological restoration, enhancement of antibody titers and helper lymphocyte proliferation were noted (Han *et al*, 2005; Liou *et al*, 2005; Sun *et al*, 2006; Yang *et al*, 2007a), there was also a significant capacity to prevent influenza (Scaglione *et al*, 1996). *In vivo* studies of *wuweizu* and *hawthorn* also showed antioxidant activity (Ma *et al*, 2006) and enhancement of phagocytic activity with agglutination titers (Xue *et al*, 2008), respectively. A Chinese safety and toxicity study of CKBM-A01 in rats and humans suggested the product was safe (LD_{50} > 21,500 mg/kg), and was efficacious in increasing CD4 cell counts (unpublished data). Regarding adverse effects, a prospective controlled trial in rats showed no difference in weight or change in hematological, hepatic, renal or reproductive parameters after 14 and 30 days of observation between the treatment and control groups, respectively. Autopsy findings of major organs demonstrated no abnormalities (unpublished data). An unpublished open study in humans conducted in Beijing, China, demonstrated no significant adverse effects among 20 male and female Chinese HIV/AIDS cases, and up to 75% had an increase in CD_4 cell counts >50 cells/μl after 3 months of treatment among patients with baseline CD4 cell counts >50 cells/μl. Thirty to 75% of patients reported improvement in lethargy and gastrointestinal symptoms, including diarrhea and lack of appetite.

In our study, no patients had evidence of the inhibitory effects on HIV or significant increases in CD4 cell counts due to CKBM-A01, as was found in previous herbal drug trials (Burack *et al*, 1996; Weber *et al*, 1999). The inconsistent findings from studies using animal models (Kim *et al*, 1990; Yang *et al*, 1990, 2007b) should prompt evaluation of dosages, different formulas, and study duration for future studies of herbal medicines. The periodic median CD4 cell counts tended to decrease every 3 months during the study. The change in CD4 counts may be due to the natural progression of HIV infection. However, immunological function might have been in the process of being restored during the study, supported by positive skin DTH reactogenicity at the end of the study, which could be affected by CKBM-AO1, since there is a time-dependent sequential loss of T-helper-cell function, which progresses from a loss of response to recall antigens to the loss of lymphocyte mitogenic response (Shearer *et al*, 1991). No clinical deterioration was detected during follow-up, which could support the effect of CKBM-A01 on preventing disease progression. Although response to at least one antigen by DTH is considered to be competent cellular immunity to recall the exposed pro-

tein, we could not ignore the rather low PPD response rate in the Thai population who are vaccinated with BCG (100% coverage). The cutaneous anergy rate to tuberculin PPD in this study was similar to other studies (Klein *et al*, 1999; Matee *et al*, 2007; Swaminathan *et al*, 2007). The clone could have been deleted or inactivated before HIV infection and should be interpreted with caution as a diagnostic test for tuberculosis.

CKBM-A01 is safe and well-tolerated because only mild drug related adverse events were reported and no one stopped the drug due to intolerance. The mildly increased bowel movements commonly found in this study are mentioned in another herbal medicine trial (Weber *et al*, 1999) and may be a common side-effect of herbal medicines. A decreased number of common colds was reported in study subjects, including those with a history of chronic rhinosinusitis, which is compatible with a previous open study of CKBM-A01 and may be due to positive immunological effects. A well-designed, placebo-controlled trial for a longer period needs to be carried out to evaluate this. Perception of wellbeing showed some improvement, though no significant difference was detected with QoL assessment during the study, as in other studies of Chinese herbal medicine (Wang *et al*, 2002; Maek-a-nantawat *et al*, 2003; Sugimoto *et al*, 2005). The potential of a new herbal treatment would itself result in psychological improvement and the expectation of improved disease outcomes.

The tolerability and safety of the Chinese herbal medicine CKBM-A01 and the lack of clinical deterioration (such as opportunistic infections) does not support or preclude the use of CKBM-A01 alone in asymptomatic HIV infected individuals with higher CD4 counts who do not meet criteria for antiretroviral drugs. However, herbal drugs may be used as an adjunct therapy in these patients for which further evaluation is needed.

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