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Double Blind Placebo Controlled Prospective Trial To Investigate The Effect Of Cordyceps Sinensis Supplementation In Minimizing Anxiety, Depression And Fatigue Associated With Chronic Hepatitis C

Submitted by:

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(alphabetical order)

Many patients have severely impaired measurements of quality of life-a prominent complaint being fatigue. There is no relationship between the severity of the liver disease and symptoms. In patients with significant liver disease, successful antiviral treatment is usually followed by marked symptomatic improvement. Many patients, however, have severe symptoms but minor liver disease and they do not qualify under current guidelines for antiviral therapy.

Patients that do not qualify for antiviral therapy are not always assured of the benign nature of their disease and many remain symptomatic. This leads many to suffer from stress associated with the knowledge of having chronic hepatitis C infection.

This stress can lead to depression. Depression tends to be associated with Th2 mediated disorders and such disorders result from a lack of Th1 cytokine immune response. The dominance of the Th2 response may result from a suppression of the Th1 response or a failure of upregulation modulated by the disease process itself. In certain disorders the Th1/Th2 ratio varies as the disease progresses indicating that this immune modulation is complex/changing and of great importance in defining the disease experienced by an individual.

The Th2 dominant state is associated with lower natural killer cell activity; low production of CD4, Interferon Gamma and Interleukin-2, mood changes, and reduced Th1 cytokine immune response activity.

There is recent evidence to suggest that mushroom nutrition (non-extracted,Coriolus versicolor)) may improve mood and thereby fatigue in patients with chronic fatigue syndrome and the HIV virus (1) (2). These improvement in symptoms has been linked to an apparent shift from a predominant Th2 immune response to a Th1 cytokine profile in these patients .

Furthermore, in Taiwan, researchers have suggested that Cordyceps sinensis (extracted) may modulate Th1 and Th2 cell functions in bronchoalveolar lavage fluids with relation to asthma, by reducing lung inflammation in the bronchial airway (3). There are open label trials with Cordyceps sinensis in chronic liver disease suggesting improvement in mental state (i.e. depression), fatigue symptoms and liver function.(4)

We propose a prospective, double blind, placebo controlled trial of Cordyceps sinensis supplementation (non-extracted) in adult patients with chronic hepatitis C. The study will measure fatigue, anxiety and depression and general health status parameters and will correlate changes in these symptoms with changes in immune function while on treatment. Immune markers to be measured will include: natural killer cell activity, and changes in both interferon Gamma and

Interleukin 2 production. As part of the study progressive measurements of both liver function and viral load will be taken.

The primary aim of this study is to determine whether Cordyceps sinensis supplementation (non-extracted) in patients with chronic hepatitis C reverses a switch in Th1 to Th2 immune response as evidenced by a change in the cytokine profile of these patients while on supplementation.

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(1) Dr.Jean Monro from the Breakspear Hospital using Coriolus versicolor supplementation over an eight week period, detected a significant increase in both NK cell count and NK cell activity in 60 Chronic Fatigue Syndrome patients. (To be published in 2002).

(2) Effectiveness of Coriolus versicolor Supplementation in the Treatment of Secondary Phanomena Associated with HIV Dr.Grazia Rotolo, Pzza San Theodoro 27100, Paivia Italy. Presented at the 10th International Symposium on Mucosal Immunology, Amsterdam, 28/6/99.
http://www.mycologyresearch.com (R&D Section)

(3) Regulation of bronchoalveolar lavage fluids cell function by the Immunomodulatory agents from Cordyceps sinensis.-Kuo YC, Tsai WJ, Wang JY, Chang SC, Lin CY, Shiao MS. Life Sci 2001 Jan 19;68(9):1067-82-National Research Institute of Chinese Medicine, Taipei, Taiwan. kuo911@cma23.nricm.edu.tw

(4) John Tindall, who founded the Gateway Clinic in 1989 (a NHS Trust outpatient clinic focused on drug and alcohol addiction) was one of the first to utilize Cordyceps sinensis supplementation in the United Kingdom to reduce fatigue in chronic Hepatitis C patients.

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Cordyceps sinensis tablets and placebos will be provided by Mycology Research Laboratories Ltd. http://www.mycologyresearch.com

ABSTRACT

DOUBLE BLIND PLACEBO CONTROLLED PROSPECTIVE TRIAL TO INVESTIGATE THE EFFECT OF CORDYCEPS SINENSIS SUPPLEMENTATION IN MINIMIZING ANXIETY, DEPRESSION AND FATIGUE ASSOCIATED WITH CHRONIC HEPATITIS C

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Many patients have severely impaired measurements of quality of life-a prominent complaint being fatigue. There is no relationship between the severity of the liver disease and symptoms. In patients with significant liver disease, successful antiviral treatment is usually followed by marked symptomatic improvement. Many patients, however, have severe symptoms but minor liver disease and they do not qualify under current guidelines for antiviral therapy.

Patients that do not qualify for antiviral therapy are not always assured of the benign nature of their disease and many remain symptomatic. This leads many to suffer from stress associated with the knowledge of having chronic hepatitis C infection.

This stress can lead to depression. Depression tends to be associated with Th2 mediated disorders and such disorders result from a lack of Th1 cytokine immune response. The dominance of the Th2 response may result from a suppression of the Th1 response or a failure of upregulation modulated by the disease process itself. In certain disorders the Th1/Th2 ratio varies as the disease progresses indicating that this immune modulation is complex/changing and of great importance in defining the disease experienced by an individual.

The Th2 dominant state is associated with lower natural killer cell activity; low production of CD4, Interferon Gamma and Interleukin-2, mood changes, and reduced Th1 cytokine immune response activity.

There is recent evidence to suggest that mushroom nutrition (non-extracted,Coriolus versicolor)) may improve mood and thereby fatigue in patients with chronic fatigue syndrome and the HIV virus (1) (2). These improvement in symptoms has been linked to an apparent shift from a predominant Th2 immune response to a Th1 cytokine profile in these patient groups.

Furthermore, in Taiwan, researchers have suggested that Cordyceps sinensis (extracted) may modulate Th1 and Th2 cell functions in bronchoalveolar lavage fluids with relation to asthma, by reducing lung inflammation in the bronchial airway (3). There are open label trials with Cordyceps sinensis in chronic liver disease suggesting improvement in mental state (i.e. depression), fatigue symptoms and liver function.(4)

We propose a prospective, double blind, placebo controlled trial of Cordyceps sinensis supplementation (non-extracted) in adult patients with chronic hepatitis C. The study will measure fatigue, anxiety and depression and general health status parameters and will correlate changes in these symptoms with changes in immune function while on treatment. Immune markers to be measured will include: natural killer cell activity, and changes in both interferon Gamma and Interleukin 2 production. As part of the protocol, progressive measurements of both liver function and viral load will be taken.

The primary aim of this study is to determine whether Cordyceps sinensis supplementation (non-extracted) in patients with chronic hepatitis C reverses a switch in Th1 to Th2 immune response as evidenced by a change in the cytokine profile of these patients while on supplementation.

SYNOPSIS OF PROTOCOL

OBJECTIVES: The primary aim of this study is to determine whether 3 grams per day of Cordyceps sinensis supplementation (non-extracted) when provided to patients with chronic hepatitis C will reverse a switch in Th1 to Th2 immune response (within 120 days) as evidenced by a change in the cytokine profile of these patients; thereby reducing anxiety, depression and fatigue associated with chronic hepatitis C virus.

PRIMARY MEASURES:
1) The fatigue scale score sheet will be completed at the baseline and at 120 days while still receiving mushroom supplementation.

2) The hospital anxiety and depression score (HAD) will be completed at baseline and 120 days.

3) SF-36 quality of life scale and an additional 8 questions relevant to Hepatitis quality of life concern will be completed at baseline and 120 days (reference for this is Bayliss MS Gandek B, Bungay KM et al Quality of Life Research 7:39-55 1998) after initial supplementation period.

SECONDARY MEASURES:
1) Blood tests for full blood count and liver function tests will be undertaken at baseline, and at 60 and at 120 days after initial supplementation period Quality of life of client, assessed by means of questionnaires.

2) Immunological tests for natural killer (NK) cell activity, CD4 lymphocyte levels, and measures of serum Interferon Gamma and Interleukin-2 and stimulated lymphocyte production of these cytokines will be undertaken at baseline, and at 60 and 120 days after initial supplementation.

3) Quantitative HCV RNA will be measured at baseline and at 60 days and at 120 days after initial supplementation.

4) Clinical examination and weight at baseline and at 60 days and 120 days after initial supplementation.

STUDY DESIGN:
Parallel group study, randomized with placebo. Study to be conducted in accordance with the Declaration of Helsinki and under the EC GCP guidelines.

STUDY POPULATION:
82 (41 x 2) volunteers aged 25 to 65 years receiving either Cordyceps sinensis (500 mg tablet) or placebo.

SUPPLEMENTATION:
Cordyceps sinensis biomass powder containing the mycelium and young fruiting bodies (primordia) tableted to pharmaceutical GMP standards into 500 mg tablets (ML 1308).

SAFETY ASSESSMENT:
Clinical safety (physical examination, vital signs) and laboratory safety, pre-dose and post study period. Adverse events will be monitored for the whole of the study period.

STUDY PROCEDURE:
Eight-two (82) patients in three separate centres with chronic hepatitis C (CHC) will be randomized to receive Cordyceps sinensis tablets (500mg) 3 tablets in the morning (30 minutes before breakfast) and 3 tablets in afternoon (30 minutes before dinner) or a matching placebo.

STUDY DURATION:
The duration of supplementation will be 120 days. The study is planned to start in June 2002 and to finish in October 2002 with a follow up of clinical data up to January 2003

DATA ANALYSIS:
Safety, adverse events and descriptive statistics

DEFINITION OF SUCCESS PARAMETERS:
1). Where scales of symptoms are used, improvement will be defined as a fall of 20 or more in 4 or more measures used in each of the scales. Failure to achieve a fall greater than 20 points in 4 measures will be regarded as a failure to respond to the supplementation. In fatigue scale scoring, if in four categories, the patient improved by 20 points or more, the patient would be considered a "responder".

2.) Changes in liver function and in viral load will be evaluated using the student t test. P values <0.05 will be taken as significant. In evaluating the viral response to supplementation it is proposed that a fall of <10% from the initial level will be regarded as non significant.

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