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Arabinoxylan rice bran (Biobran) suppresses the viremia level in patients with chronic HCV infection: A randomized trial*

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Abstract

Current treatments for Hepatitis C virus (HCV) have severe side effects and are very expensive. There is a need to explore effective natural therapies against HCV that are less toxic and more cost-effective. In the current study, 37 chronic HCV patients were randomized into two groups and treated with either pegylated interferon (PEG IFN) plus ribavirin (n = 21) or Biobran, an arabinoxylan from rice bran (1 g/day) (n = 16). We examined viremia, liver enzymes, interferon-γ (IFN-γ) levels in serum, and toxicity before and three months after treatment. Both groups showed a significant and similar reduction in viral load after three months of treatment relative to the baseline viral load (P <0.05). In addition, treatment with Biobran resulted in a significant increase in the level of IFN-γ (P <0.001). Patients in the PEG IFN plus ribavirin group showed fever, anemia, thrombocytopenia, and easy fatigue. Patients in the Biobran group showed no side effects and reported good health. We conclude that Biobran is a potential novel therapeutic regimen that has a similar effect to PEG IFN plus ribavirin and is safe and cost-effective in the treatment of chronic HCV. Our finding of Biobran's efficacy against HCV infection warrants further investigation in multiple clinical trials (Clinical Trials Registration: NCT02690103).

Keywords

arabinoxylan, Biobran, Hepatitis C virus (HCV), pegylated interferon (PEG IFN), viremia

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Introduction

Hepatitis C virus (HCV) has infected approximately 130–150 million people worldwide (about 2–3% of the world's population) with approximately 700,000 deaths each year[1] and is a major cause of life-threatening liver diseases, such as liver cirrhosis and hepatocellular carcinoma. There is a great variation in HCV prevalence around the world, ranging from <1% of a country's population to well over 10%. The Centers for Disease Control and Prevention (CDC) states that the prevalence of HCV is highest in Egypt, with approximately 10% of the population being infected.[1] Studies also show that HCV has several genotypes. Genotype 1 is most common in the USA and Japan, while genotype 4 is most common in Egypt. Chronic HCV develops in 60–85% of patients with acute HCV. Cirrhosis occurs

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in 15–30% of patients and hepatocellular carcinoma occurs in 1–3%, both of which are related to mortality of the patients. No protective vaccine is available for HCV treatment. The current treatments include pegylated interferon (PEG IFN), ribavirin, boceprevir, telaprevir, and Sofosbuvir (sovaldi). PEG IFN activates cellular antiviral responses; however, approximately 50% of responders will relapse upon withdrawal of treatment. Ribavirin acts by unknown mechanisms, but may be responsible for the direct inhibition of RNA-dependent RNA polymerase (RdRp) or alteration of the nucleotide pool needed for replication. Several studies have shown that the combination of PEG IFN and ribavirin is more effective than either treatment alone. Boceprevir and telaprevir are both new protease inhibitors and act on viral protease NS3-4a, specifically for genotype 1 and are used either alone or in combination with interferon. Finally, Sofosbuvir is a nucleotide analog that is used with other drugs, such as ribavirin for genotypes 2 and 3 and PEG IFN for genotypes 1 and 4. Sofosbuvir inhibits RNA polymerase (NS5B Inhibitor), which the hepatitis virus uses to replicate its RNA.

The above synthetic antiviral treatments for HCV have many side effects, and some of the drugs, such as Sofosbuvir, are very expensive. Therefore, there is a need to explore the therapeutic applications of natural products that are nontoxic, affordable, and exert an anti-HCV effect. Biobran is a modified rice bran extract that contains polysaccharide β1, 4-xylopyronase hemicellulose. The main chemical structure of Biobran is an arabinoxylan, with a xylose in its main chain and an arabinose polymer in its side chain.[2] Biobran is a potent biological response modifier (BRM) known to enhance NK cell activity,[3–6] activate dendritic cells (DCs),[7–9] modulate interferon production,[10] and enhance intracellular killing of microbes by human phagocytic cells.[11] Previous research has shown the potential of Biobran as a protector against different types of malignancies[12] including Ehrlich carcinoma-associated oxidative stress,[13] γ-radiation,[14] and HIV activity.[2]

In the current study, we examined the anti-HCV effect of MGN-3/Biobran. We present the preliminary investigation of Biobran's ability to restrict viremia in patients with chronic HCV. In addition, we examined the effect of Biobran on liver enzymes and inflammation and assessed its side effects.

Subjects and methods

Biobran

Biobran is a denatured hemicellulose that is obtained by reacting rice bran hemicellulose with multiple carbohydrate hydrolyzing enzymes from Shiitake mushrooms. It is a polysaccharide that contains ß-1, 3-glucans, and activated hemicellulose.[2] Biobran was kindly provided by Daiwa Pharmaceuticals Co. Ltd., Tokyo, Japan.

Inclusion/exclusion criteria for patients

Inclusion criteria were:

1. Age range of 18–65 years and either sex.
2. Evidence of post-HCV chronic active hepatitis proven by liver biopsy.
3. Willing to participate in the study and give a written consent.

Exclusion criteria were:

1. Patients with F0 and F4 on liver histopathogy.
2. Presence of auto-immune hepatitis.
3. Pregnant and lactating women.
4. Marked portal hypertension and pancytopenia.
5. Presence of major psychological insult.
6. Presence of other infections such as HBV and HIV.
7. Patients receiving other anti-viral therapies.
8. Inability to give a written consent.

Study design

For the randomized trial, we selected 37 patients who had been admitted to The Kasr El Einy Hospital in Cairo, Egypt. The patients had been diagnosed with genotype 4 HCV. The study was approved by Cairo University Hospital, Cairo, Egypt and by Institutional Review Board (IRB) at Charles R Drew University of Medicine and Science (CDU), Los Angeles, CA, USA. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in the prior approval by Cairo University, Al Kasr El Einy Hospital at Cairo, Egypt and by the IRB at Cairo University, Egypt and CDU, Los Angeles, CA, USA.

Table 1. Clinical characteristics of HCV patients treated with PEG IFN plus ribavirin (control) vs. Biobran.

Characteristics	PEG IFN + ribavirin (mean ± SD or %)	Biobran (mean ± SD or %)
Patients (n)	21	16
Age (years)	39.8 ± 10.8	45.3 ± 12.1
Sex (% male)	66.7%	56.3%
AFP (ng/mL)	8.3 ± 4.8	9.8 ± 6.0
TLC (/cmm)	5.6 ± 2.0	5.8 ± 1.6
PLT (/cmm)	175.3 ± 44.2	203.9 ± 58.4
Hb (g/dl)	13.9 ± 1.7	13.8 ± 1.7
Cholesterol (mg/dl)	159.5 ± 25.7	164.8 ± 42.2
TGs* (mg/dl)	149.3 ± 27.1	110.4 ± 27.1
HbA1c* (%)	6.5 ± 0.5	5.9 ± 1.0
Creatinine* (mg/dl)	0.7 ± 0.2	0.9 ± 0.1
Albumin (g/dL)	4.2 ± 0.4	3.9 ± 0.4
Bilirubin (mg/dl)	0.9 ± 0.3	0.8 ± 0.3
INR (ratio)	1.1 ± 0.1	1.0 ± 0.1
RBG (mg/dL)	96.3 ± 11.6	103.8 ± 32.5

*Statistically significant (P <0.05).

Patients

Thirty-seven patients (23 men, 14 women; age range, 15–69 years) with HCV (genotype 4) participated in the current study. Informed consent was obtained from all subjects. The patients were randomly assigned to two groups: the Biobran (intervention) group (n = 16) and the PEG IFN plus ribavirin (control) group (n = 21). Prior to treatment, clinical characteristics were determined for the patients in each group (Table 1). The clinical characteristics of the HCV patients were investigated for hepatitis C, alpha-fetoprotein (AFP) levels, total leucocyte count (TLC), platelet (PLT) count, hemoglobin (Hb) levels, cholesterol levels, triglyceride (TG) levels, glycated hemoglobin (HbA1c) levels, creatinine levels, albumin levels, bilirubin levels, blood clotting using the international normalized ratio (INR), and random blood sugar (RBG).

Protocol for determination of lymphocyte subsets

Fresh peripheral blood was collected on EDTA and total white blood cell (WBC) count was performed using Celltac α – 6400 series-Nihon Khoden. Differential WBC count was done on Leishman stained blood films. The whole blood sample was incubated with anti-human CD16-FITC and anti-human CD56-PE monoclonal antibody reagents at 4°C. Nucleated cells were separated from red blood cells and cell yield was determined with automated cell counter. Samples were tested using Beckman Coulter EPICS XL flow cytometer to determine lymphocyte subsets, CD16+ CD56–, CD16– CD56+, and CD16+ CD56+ cells.

Procedures

Patients in the control group (age 40 ± 11 years; 14 men, 7 women) were treated with 180 μg of PEG IFN (Pegasys-Roche) subcutaneously weekly for three months. In addition, they were given ribavirin according to their body weight (1200 mg for those over 75 kg and 1000 mg for those under 75 kg). The Biobran group (age 45 ± 12 years; 9 men, 7 women) was treated with Biobran, at a dose of 1 g per day, allocated in packets, taken orally with meals for the three-month duration of the study.

Viral load levels, toxicity, liver enzyme levels, interferon-γ (IFN-γ) levels, and percentage of lymphocyte subsets were examined before and three months after treatment. Viral load was examined by quantitative polymerase chain reaction (PCR) test using COBAS® TaqMan® Analyzer (Roche Corporation). IFN-γ, AFP, ALT, and AST levels were analyzed using specific Elisa Kits, which were performed by Spectrum Chemical Manufacturing Corporation, Gardena, CA, USA, and toxicity was assessed by a questionnaire, physician observation, and laboratory results.

Lymphocyte subsets and IFN-γ were only examined in the Biobran group at baseline and three months after treatment.

Table 2. Level of viral load and liver enzymes at baseline and three months in both groups.

Parameter	PEG IFN + ribavirin			Biobran		
	Baseline	After 3 months	*P* value	Baseline	After 3 months	*P* value
Viral load (IU/mL) (median)	300,000	16	0.001	224,500	70,150	0.023
ALT (U/L) (mean ± SD)	59.7 ± 43.3	42.8 ± 24.9	0.007	40.5 ± 18.5	49.1 ± 21.7	0.096
AST(U/L) (mean ± SD)	49.2 ± 20.5	44.6 ± 14.0	0.06	42.0 ± 15.0	46.6 ± 19.1	0.426

Statistical analysis

Descriptive statistics were used to characterize the study population. Categorical variables were presented as number and percent. Continuous variables were presented as mean and standard deviation. To test the statistical differences between the Biobran (intervention) group and the control group, we used the Chi-square test for categorical variables, t-test for normally distributed continuous variables, and Mann–Whitney U test for non-normally distributed continuous variables. Paired t-test was used to test the statistical difference between the baseline and the values at three months post treatment in each group for the normally distributed continuous variables. For non-normally distributed variables, we used the non-parametric median test—Wilcoxon signed rank test. To test the statistical difference in baseline viral load, three-month post-treatment viral load, and the reduction in viral load three months post treatment between the Biobran (intervention) group and the control group, we used the non-parametric Mann–Whitney U test. Data were analyzed using SPSS version 22 and STATA version 14 and P values <0.05 were considered statistically significant.

Results

Clinical characteristics of HCV patients

Table 1 summarizes the range of measured characteristics for patients in the control group and the Biobran group. The Biobran group was statistically different from the control (PEG IFN plus ribavirin) group in the baseline levels of three out of 14 variables: TG, HbA1c, and creatinine (P <0.05). There was no statistically significant difference between the two groups (P >0.05) in all other baseline variables.

Viremia level

The primary outcome was the viremia level in patients after treatment. The effect of Biobran and PEG IFN plus ribavirin on the viral level is illustrated in Table 2. PCR levels before and three months after treatment showed that patients given Biobran demonstrated significant reduction in the viral load relative to the baseline value (median level of viral load: median pre = 224,500 and median at three months = 70,150, median difference = −35,200; P = 0.023). Patients given PEG IFN plus ribavirin demonstrated a significant reduction in the viral load relative to the baseline value (median level of viral load: median pre = 300,000, median at three months =16, median difference = −153,984; P = 0.001). Of the 21 patients in the PEG IFN plus ribavirin group, 11 patients (52.4%) had viral loads that were very low and undetermined (i.e. the level of viral load is 16).

Patients in both groups showed significant reduction in the viral load relative to the baseline value (P <0.05). There is no statistical difference between the median viral load of the two groups in the baseline (P = 0.175). There is no statistical difference between the median viral load of two groups in the PCR after three months of treatment (P = 0.377) and the median reduction in the viral load relative to baseline (P = 0.235).

Liver enzymes

Studies with liver enzymes (ALT and AST) are illustrated in Table 2. Treatment with Biobran after three months showed an increase of 21.3% in ALT level and 11.0% in AST level compared to the baseline values but they were not statistically significant (P >0.05). In contrast, patients treated with PEG IFN plus ribavirin showed a decrease in both enzymes at three months after treatment and it was statistically significant only for ALT (P = 0.007).

Interferon-γ levels

IFN-γ levels were examined at baseline and three months for the Biobran group. Results in Figure 1 showed the levels of IFN-γ among 16 patients as

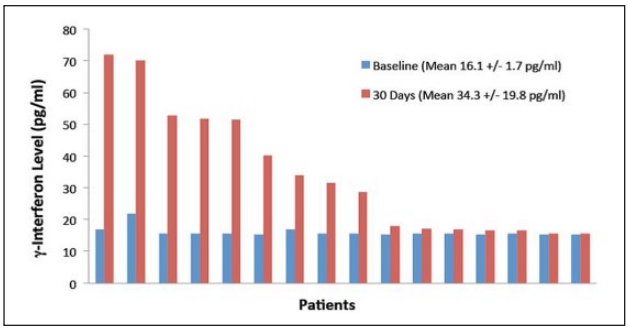

Figure 1. The levels of IFN-γ among patients on Biobran before and three months after treatment (n = 16).

Table 3. Lymphocyte subsets at baseline and three months for the Biobran group.

Lymphocyte subsets	Biobran		
Cells (%)	Baseline (mean ± SD)	After 3 months (mean ± SD)	*P* value
CD16+ CD56–	7.8 ± 4.8	8.8 ± 4.3	0.07
CD16– CD56+	5.6 ± 2.8	5.3 ± 3.0	0.96
CD16+ CD56+	11.5 ± 5.1	10.2 ± 5.6	0.36

follows: 9/16 patients (56.3%) showed a 2–4.2-fold increase, 5/16 patients (31.3%) showed a slight increase, and 2/16 patients (12.5%) showed no increase. Overall, the mean baseline value of IFN-γ was 16.1 ± 1.7 pg/mL and after three months it was 34.4 ± 19.8 pg/mL, which represents a two-fold increase at three months compared to the baseline value (P <0.001).

Lymphocyte subsets

Lymphocyte subsets were examined at baseline and three months for the Biobran group. Results in Table 3 showed that there is no significant change in the CD16+ CD56–, CD16– CD56+, and CD16+ CD56+ at three months compared to the baseline value (P >0.05).

Toxicity

The toxicity of Biobran and PEG IFN plus ribavirin was evaluated by a questionnaire, medical doctor observation, and laboratory results. Patients treated with PEG IFN plus ribavirin showed easy fatigue, fever, digestive disorders, weight loss, dry cough, hepatomegaly, anemia, thrombocytopenia, headache, and body ache. In contrast, patients treated with Biobran showed no side effects and reported good health. Table 4 shows more details of the symptoms reported by patients in both groups.

Cost

The cost of anti-HCV treatments varies significantly. Biobran can cost less than $1,000 for a three-month supply, while on the other hand, anti-HCV drugs can be much more expensive. For example, a 12-week supply of PEG IFN plus ribavirin can cost patients in Egypt $3000 per month and American patients up to $10,000. The cost of Sofosbuvir is even more prohibitive, at $84,000 for a three-month supply.

Discussion

The present study on the anti-HCV activity of Biobran was motivated by previous studies that showed the antiviral activity of Biobran. For example, Biobran was shown to exert anti-HIV activity by inhibiting HIV-1 replication as shown in peripheral blood mononuclear cells (PBMCs) from healthy subjects infected with HIV-1 SF strain.[15] Biobran inhibited syncytia formation in both AIDS patients as well as PBMC infected healthy subjects.[2,15] Furthermore, Biobran has been shown to prevent symptoms of the common cold in elderly people, with a significant decrease in the common cold syndrome score (CCS) for cough, malaise, fever, sore throat, and nasal discharge/sneezing. The total CCS for the elderly taking Biobran was about threefold lower than the total score without Biobran ingestion.[16] These results encouraged us to pursue Biobran's potential effect on restricting viremia in patients with chronic HCV.

The results in this article showed that patients treated with Biobran demonstrated a significant reduction in the viral load after three months of treatment relative to the baseline viral load. The reductions in the viral load of the Biobran group was similar with that observed in the control group, receiving standard treatment of PEG IFN plus ribavirin (P >0.05).

Additionally, patients treated with PEG IFN plus ribavirin showed a decrease in both liver enzymes after treatment, in accordance with earlier study by Hui et al. who found a decrease in ALT levels at three months after treatment with PEG

Table 4. Clinical findings of HCV patients treated with PEG IFN plus ribavirin or Biobran.

Symptoms	PEG IFN + ribavirin	Biobran
Fatigue	10 (47.6%)	0
Right upper quadrant pain	8 (38.1%)	0
Fever (Low Grade to High Grade)	20 (95.2%)	0
Digestive disorder (dyspepsia, anorexia, abdominal discomfort)	20 (95.2%)	0
Weight loss*	10 (47.6%)	0
Sore throat/respiratory infection	3 (14.3%)	0
Hepatomegaly	15 (71.4%)	11 (68.8%)
No symptom	5 (23.8%)	0

*Weight loss was defined by any level of weight loss after being introduced into the study.

IFN plus ribavirin.[17] The decrease appears to continue for longer periods as well, as shown by Levent et al.[18] On the other hand, those treated with Biobran showed an insignificant change in these two enzymes.

The precise mechanisms by which Biobran exerts its inhibitory effects on HCV remains to be studied. HCV enters into cells by binding to scavenger receptors type B1; its expression is downregulated by lipopolysaccharide.[19–23] Since Biobran is a polysaccharide and may function like other polysaccharides extracted from fungi and bacteria, it is possible that Biobran inhibits HCV replication by downregulating the HCV receptors. Alternatively, Biobran might act as a therapeutic vaccine by boosting host protective cell mediated immune responses against HCV and thus help to decrease the viral load. This view is supported in part by the observation in this study that most patients treated with Biobran show increased levels of IFN-γ. Studies have shown IFN-γ to be a potent inhibitor for the virus replication.[24,25] In addition, we and others have previously shown that Biobran modulates different immune cells[12] such as CD4+ and CD8+ T cells[8–10] and NK cells,[3–6] both in vitro and in vivo. These immune cells are well-known to play a major role in anti-viral infection including HCV.

It is of interest to note that the Biobran group demonstrated no side effects and patients reported good health, while among the PEG IFN plus ribavirin group there was fever, anemia, and thrombocytopenia and the patients reported easy fatigue. Furthermore, while the cost of standard care therapy (PEG IFN plus ribavirin) for treating chronic HCV genotype 4 in Egypt is $3000 for a three-month supply and can be as high as $10,000 in the USA, the cost of a three-month supply of Biobran is less than $1,000.

We conclude that Biobran is a potential novel therapeutic regimen that is low-cost, safe, and effective in the treatment of chronic HCV. Further studies are warranted to establish its efficacy in large number of patients infected with HCV and for longer periods of time.

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Declaration of conflicting interests

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