Biobran/MGN-3, Arabinoxylan Rice Bran, for the Treatment of Chronic Hepatitis C

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OUTLINE

1. HCV Background
   a. Types of HCV, HCV Prevalence, Cost, Toxicity

2. Biobran anti-HIV activity

3. Biobran anti-HCV activity
   a. Study Design
   b. Results

4. Possible Mechanisms
   a. NK, CD8+ T cells and Dendritic cell (DC) activation
   b. Interferon production

5. The Uniqueness of Biobran

6. Acknowledgements/Conclusion
Hepatitis C virus (HCV)

Model of HCV
- E Proteins
- Lipid Bilayer
- Capsid
- Enveloped RNA

Cryo-EM Image*
- 7 Å thick slice of HCV
- Red Arrows: Lipid Bilayer
- Blue Arrow: Capsid
- Black Arrow: E1/E2 Glycoproteins

Cross-section model and electron microscope image of HCV

• Genotype Type 1 is most common in US
• Genotype Type 4 is most common in Egypt
## HCV Prevalence & Deaths per Year

<table>
<thead>
<tr>
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<th>Worldwide</th>
<th>USA*</th>
<th>Egypt**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence</strong></td>
<td>185 Million</td>
<td>3.9 Million</td>
<td>12 Million</td>
</tr>
<tr>
<td><strong>Deaths/Year</strong></td>
<td>&gt; 350,000</td>
<td>17,000 (2012)</td>
<td>40,000</td>
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</table>


The Natural Progress of HCV Infection

Acute HCV infection can resolve in 15-40% of cases. About 60-85% of cases progress to chronic infection. Of those, about 15-30% will develop cirrhosis, and 1-3% of cirrhosis cases will progress to hepatocellular carcinoma.

Time (years): 0, 10, 20, 30.
Treatment for Hepatitis C Virus Infections

• No protective vaccine available.

• Interferon (Pegylated IFN)
  – Pegylated IFN is used due to increased stability in vivo. Activates cellular antiviral responses. ~50% of responders will relapse upon withdrawal of treatment.

• Ribavirin
  – Mechanism unknown, but may be direct inhibition of RDRP or alteration of nucleotide pool needed for replication. *The combination of interferon and ribavirin* is more effective than interferon alone.

• Sovaldi
  – A nucleotide analog that is used with other drugs such as Riba for genotypes 2 and 3, and with pegylated IFN for genotypes 1 and 4. It inhibits RNA polymerase that the hepatitis virus uses to replicate its RNA.
Toxicity of Treatment for HCV Infections

Pegylated IFN
- Injection site inflammation
- Fatigue
- Headache
- Rigors
- Fever
- Nausea
- Myalgia
- Anxiety or emotional lability/irritability
- Hematologic toxicity: neutropenia/thrombocytopenia
- Ophthalmologic disorders

Ribavirin
- Hemolytic anemia
- Cardiac disease
- Myocardial infarction
- Birth defects

Sovaldi
- Fatigue
- Headache
- Birth defects

http://www.hepatitisc.uw.edu/page/treatment/drugs/peginterferon-alfa-drug
http://www.hepatitisc.uw.edu/page/treatment/drugs/ribavirin-drug
http://www.hepatitisc.uw.edu/page/treatment/drugs/sofosbuvir-drug
Due to the **high-cost** and **severe side effects** of current HCV treatments, we are in great need of finding new agents that are less expensive and less/non-toxic AND highly effective in combating the Hepatitis C Virus.
Biobran/MGN-3
Arabinoxylan rice bran
What is arabinoxylan (Biobran/MGN-3)?

• Biobran is a denatured hemicellulose, which is obtained by reacting rice bran hemicellulose with multiple carbohydrate hydrolyzing enzymes from the Shiitake mushrooms.
• The main chemical structure of Biobran is an arabinoxylan with a xylose in its main chain and an arabinose polymer in its side chain.

Biobran Exerts Anti-Viral Activity

1- Biobran/MGN-3 Inhibits HIV-1 Replication (PBMC from healthy subjects infected with HIV)*

## 2-Biobran/MGN-3 Inhibits Syncytia Formation

### Table: MGN-3 dosage effects on Syncytia Formation

<table>
<thead>
<tr>
<th>MGN-3 dosage (µg/ml)</th>
<th>Healthy Subjects*</th>
<th>AIDS Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of SF</td>
<td>% Inhibition</td>
</tr>
<tr>
<td>0</td>
<td>42 ± 8</td>
<td>0</td>
</tr>
<tr>
<td>12.5</td>
<td>25.8 ± 7</td>
<td>38.5</td>
</tr>
<tr>
<td>25</td>
<td>21.5 ± 5</td>
<td>50</td>
</tr>
<tr>
<td>50</td>
<td>15.8 ± 4</td>
<td>62.5</td>
</tr>
<tr>
<td>100</td>
<td>10.5 ± 3</td>
<td>75</td>
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</table>

### Syncytia Formation (SF): During infection with HIV, viral fusion proteins used by the virus to enter the cell are transported to the cell surface, where they can cause the host cell membrane to fuse with neighboring cells.

* HIV-1 SF strain, HIV-1 p24 of 3000 pg/million cells. Data represents mean +/- s.d. from 5 subjects.

Ghoneum M. Anti-HIV Activity by MGN-3 *In vitro*. XI International Conference on AIDS. Vancouver July 7-12, 1996.
Purpose of the Current Study

• The ability of Biobran to exert anti-HIV activity encouraged us to pursue the current study.

• The purpose of the current study is to examine the anti-HCV effect of Biobran on viremia in clinical trials of patients with positive chronic HCV.
The study was approved by the Institutional Review Board (IRB) at:

- **Cairo University, Egypt**  
  [IRB#: A-13-3012]

- **Charles R Drew University (CDU), Los Angeles CA, USA**  
  [IRB #: 14-07-2431-01]
Study Design
[Randomized Control Trial]

39 HCV Patients
17 Patients (Biobran alone) 1 g/day oral
22 Patients (Control = IFN + Ribavirin)

3 Months Later
1 Viral Load Level (serum hepatitis C virus (HCV)-RNA) determined by PCR
2 Toxicity (questionnaire, MD observation, and lab results)
RESULTS

1-Viral Load
2-Toxicity
3-Cost
1- Viral Load
Biobran effect on the level of the viral load

- PCR levels before and 3 months after treatment showed that:
  - patients given Biobran demonstrated significant reduction in the viral load relative to the baseline value (p=0.023).
1- Viral Load
Interferon plus Ribavirin effect on the level of the viral load (Control group)

- PCR levels before and 3 months after treatment showed that:
  - patients given Interferon plus Ribavirin (Control group) demonstrated significant reduction in the viral load Relative to the baseline value (p=0.001).
1- Viral Load

COMPARISON BETWEEN THE TWO GROUPS

Patients in both groups showed significant reduction in the viral load relative to the baseline value.

- There is **NO** statistical difference between the median of two groups in the baseline ($p=0.851$).
- There is **NO** statistical difference between the median of two groups in the PCR after 3 months of treatment ($p=0.836$).
2- Toxicity
Evaluuated by: Questionnaire, MD observation, and lab results

<table>
<thead>
<tr>
<th>Biobran group</th>
<th>Control group (IFN-γ + Ribavirin)</th>
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<tbody>
<tr>
<td>• No side effects</td>
<td>• Fever</td>
</tr>
<tr>
<td>• Patients reported good health</td>
<td>• Anemia</td>
</tr>
<tr>
<td></td>
<td>• Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>• Dry cough</td>
</tr>
<tr>
<td></td>
<td>• Headache</td>
</tr>
<tr>
<td></td>
<td>• Body ache</td>
</tr>
<tr>
<td></td>
<td>• Patients reported easily fatigued</td>
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</table>
3- Cost of 12-Week Treatments for HCV Infections

COST of 12-Week Treatment

- Sovaldi + IFN/Riba: $94,000
- IFN + Riba: $9,000-$10,000
- Biobran: $300
Mechanisms Underlying the Anti-HCV Activity of Biobran
Biobran induces various immune cells to attack viral infected cells

1. NK cells
2. CD8+ T cells
3. DCs
4. IFN-γ

NK cells

Viral infected cell

CD4+ T cells

IFN-α

IFN-λ

3. DCs
NK/CD8+T cell activity against **target** cells
Biobran increases granular content of NK & CD8+ T cells

1. NK Cells

Bar graphs depict the percentage of CD8+ T cells expressing granzyme B. Data represent the mean ± S.E. of 5 experiments.

Biobran enhances human NK & CD8+ T cell activity

1- NK cell activity

![Graph showing NK cell activity over time with different dose levels.]

2- CD8 + T Cell activity

![Bar graph showing % lysis with CD8+ T Cell activity.]

1. Biobran primed DC-induced IFN-γ secretion by CD4+ cells

The secretion of IFN-γ in the supernatants was assessed using specific ELISA kits. The data are the mean ± SD from 4 individual experiments; *p<0.05, as compared to control DCs.

2. Biobran activated DCs secrete Type I IFN (IFN-α) and Type III IFN (IL-29/IFN-λ)

Biobran activates dendritic cells to induce a distinct profile of Type I and III IFNs cytokine secretion. Data represent the mean ± S.E. of 6 experiments. *(p<0.05) as compared to DCs alone.

While several studies have shown that a single administration of BRMs can significantly enhance NK cell activity, repeated administration of the same BRM has resulted in depression of NK cell activity, an effect known as hyporesponsiveness. The hyporesponsiveness of NK activity is a serious problem and is an associated phenomenon with many BRMs. It is interesting to note that MGN-3 was evaluated for 5 years and NK activity was maintained at a high level throughout the continuation of treatment. This suggests that Biobran does not have hyporesponsiveness.

Action of Many BRMs on NK Activity Over Time

EXCELLENT

GOOD

FAIR

POOR

Biobran

Other BRMs

NK CELL ACTIVITY (Lytic Units)

TREATMENT TIME (weeks)
Long Term (5 years) follow up of NK activity
(Data of 8 Breast Cancer Patients)
CONCLUSION
CONCLUSION

1. Biobran is a novel therapeutic regimen that is safe and effective in the treatment of chronic HCV

2. The mechanisms by which Biobran exerts its effect may involve activation of human immune cells that are known to exhibit antiviral activity.

3. Ongoing studies are designed to confirm the conclusions in larger samples and to examine the long-term effect of Biobran on the treatment and the recurrence of HCV.
Contributors

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Biobran was provided by Daiwa Pharmaceutical Co., Ltd., Tokyo, Japan.
Published articles in peer-review journals on MGN-3/Biobran


Published articles (Continued)


Published articles (Continued)


International & National Symposia
Presented Abstracts


Presented Abstracts (Continued)


