Hepatitis B & C in Bangladesh

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Associate Professor of Hepatology
Bangabandhu Sheikh Mujib Medical University
Dhaka, Bangladesh
Changing Pattern of Liver Diseases in Bangladesh

- Significantly increased: fatty liver, treatable hepatitis B
- Significantly decreased: acute hepatitis, inactive hepatitis B
- More serious liver diseases on the rise!!
HBV in Bangladesh
Epidemiology of hepatitis B virus in Bangladeshi general population

Mamun-Al Mahtab, Salimur Rahman, Md. Fazal Karim, Mobin Khan, Graham Foster, Susannah Solaiman and Shahrin Afroz

Dhaka, Bangladesh

- Sample size: 1028 apparently healthy subjects
- Method of study: Questionnaire
- Study Place: Savar, Dhaka
- Prevalence: 5.4% (2.5% of world’s HBV population)
Conventional Risk Factors

- Injection 65.8%
- Vaccination (Smallpox, Cholera) 39%
- I/V Infusion 16.5%
- Surgery 13.2%
- Dental Procedure 12.4%

Socio-Cultural Risk Factors

- Treatment from Quack 64%
- Shaving / Haircut in Barber Shop 35.3%
- Body Piercing 11.1%
- Family H/O Hepatitis 25.4%

Mahtab et. al HBPD Int. 2008
Prevalence of HBV in <5 year old Bangladeshis

- HBsAg +ve 4.2%
- Anti HBc total +ve 31.9%

- >1 family member infected 25%
  - Father only 21%
  - Mother only 13.3%
  - Child only 4.5%
  - Father + Mother 15.3%
  - Father + Child 3.8%
  - Mother + Child 2.5%
  - Father + Mother + Child 4.8%

- Exposure rate 15.7% (1 yr), 17.9% (5 yrs), 40% (adult)

Early horizontal transmission in pre-school age principal mode of HBV transmission in Bangladesh

Ahmad et. al J BSMMU 2012
History of HBV Vaccination in Bangladesh

- Universal immunization program inaugurated in Bangladesh on April 7, 1979 on World Health Day
- EPI intensification from 1985-1990; expanded nationwide
- Hepatitis B vaccine introduced in 2003
- Bangladeshi kids receive vaccines against 9 diseases namely, TB, polio, diphtheria, pertussis, tetanus, hepatitis B, H. influenza type B, measles and rubella
- Rubella vaccine is the latest to be added; pneumococcus vaccine will become 10th vaccine shortly
- Bangladesh EPI Coverage Evaluation Survey 2010
  - DPT 89.4%
  - BCG 98.9%
  - Measles 89.2%
  - HBV 89.4%
  - OPV 94.7%
  - Fully immunized 83.4%
  - Vitamin A coverage 96.0%

Source: DGHS, Bangladesh & WHO
Changing HBV Prevalence in Bangladesh

Mahtab et al. HBPD Int 2008
Islam et al. Bangladesh Med Res Coun Bul 1884
Hepatitis B Induced Liver Diseases in Bangladesh

Mahtab et al. JHPN 2008
Mahtab et al. Indian J Gastroenterol (Suppl) 2007
Afroz et al. Hepatol Int (Suppl) 2007
Mahtab et al. Hepatol Int (Suppl) 2009
HBV Related Liver Cancer: Past and Present

- Chowdhury et al JCMCTA 2009
- Mahtab et. al. Hepatol Int (Suppl) 2009
- Karim et. al. Korean J Hepatol (Suppl) 2011

<table>
<thead>
<tr>
<th>Year</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>1991-2</td>
<td>46.9%</td>
</tr>
<tr>
<td>2001-2</td>
<td>61.9%</td>
</tr>
<tr>
<td>2004-8</td>
<td>75%</td>
</tr>
<tr>
<td>2009</td>
<td>61.5%</td>
</tr>
</tbody>
</table>
Economic Burden of Hepatitis B in Bangladesh

Direct Cost

- Cost of baseline investigations USD 100 - 200/year
- Cost of follow up investigations USD 120 - 290/year

Cost of Drugs

- PEG IFN USD 2800 - 6230/6 months
- LAM USD 117/year
- ADV USD 164/year
- LdT USD 1170/year
- ETV USD 210/year
- TDV USD 304/year

Indirect Cost

- Transport, reduced work, premature death etc.
- 20% of direct cost in South Korea
- Approx. USD 1000-2900/patient/year

Mahtab et al. Hepatol Int. (Suppl) 2012
Yang et al. J Gastroenterol Hepatol. 2001
Mahtab et al. Hepatol Int. (Suppl) 2012
- Cost of Padma Bridge approx. Tk. 12,000 crores
- If 10% of Bangladeshi HBV patients receive treatment
- Approx. Tk. 6,000 crores needed per year
Liver diseases account for 8-12% admissions in Medicine wards of our public medical college hospitals

Liver diseases 3rd commonest cause of deaths in hospitals in Bangladesh

Hepatitis B & C responsible for >20,000 deaths/year in Bangladesh

Liver cancer 3rd commonest cancer in Bangladesh; next to lungs and stomach cancers
The ‘Complex Story’ of HBV
HBV in ‘Safe Blood’ Transfused in Bangladesh

- N 398
- Safe blood transfused in a tertiary hospital
- All HBsAg -ve, but 20.6% (82/398) anti-HBc +ve
- 8.5% (7/82) HBV DNA +ve
- In 6/7 ALT > ULN
- Genotype C in all

Jahan, (Mahtab) et. al  unpublished data 2014
And What May be Waiting for Them!!
Characteristics of IDAHS in Bangladesh

In a series of 702 IDAHS, 15.6-22.6% had significant hepatic necro-inflammation and 2.4-3.29% had significant hepatic fibrosis.

Biochemical, Virological, Immunological and Histopathological Features of 702 Incidentally Detected Chronic Hepatitis B Virus Carriers in Bangladesh

Mamun Al-Mahtab\textsuperscript{a}  Sheikh Mohammad Fazle Akbar\textsuperscript{d}  Salimur Rahman\textsuperscript{a}
Mohammad Kamal\textsuperscript{b}  Mohammad Sakirul Islam Khan\textsuperscript{c}

Departments of \textsuperscript{a}Hepatology and \textsuperscript{b}Pathology, Bangabandhu Sheikh Mujib Medical University, Dhaka, and
\textsuperscript{c}Department of Animal Science, Bangladesh Agricultural University, Mymensingh, Bangladesh;
\textsuperscript{d}Department of Medical Sciences, Toshiba General Hospital, Tokyo, Japan

<table>
<thead>
<tr>
<th></th>
<th>HBeAg-positive (n = 248)</th>
<th>HBeAg-negative (n = 454)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV DNA &lt; 1 $\times 10^5$ copies/ml</td>
<td>19 (7.7%)</td>
<td>325 (71.6%)</td>
</tr>
<tr>
<td>HBV DNA &gt; 1 $\times 10^5$ copies/ml</td>
<td>229 (92.3%)</td>
<td>129 (28.4%)</td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq 42$ U/l</td>
<td>107 (43.1%)</td>
<td>248 (54.6%)</td>
</tr>
<tr>
<td>43–84 U/l (twice of ULN)</td>
<td>104 (41.9%)</td>
<td>172 (37.9%)</td>
</tr>
<tr>
<td>85–126 U/l (thrice of ULN)</td>
<td>25 (10.1%)</td>
<td>23 (5%)</td>
</tr>
<tr>
<td>&gt;126 U/l</td>
<td>12 (4.8%)</td>
<td>11 (2.4%)</td>
</tr>
<tr>
<td>Liver histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extent of hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAI-N1 $\leq 3$</td>
<td>76 (30.6%)</td>
<td>216 (47.6%)</td>
</tr>
<tr>
<td>HAI-N1 4–6</td>
<td>116 (46.8%)</td>
<td>167 (36.8%)</td>
</tr>
<tr>
<td>HAI-N1 $\geq 7$</td>
<td>56 (22.6%)</td>
<td>71 (15.6%)</td>
</tr>
<tr>
<td>Extent of fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAI-F0</td>
<td>20 (8.1%)</td>
<td>49 (10.8%)</td>
</tr>
<tr>
<td>HAI-F1</td>
<td>166 (66.9%)</td>
<td>315 (69.3%)</td>
</tr>
<tr>
<td>HAI-F3</td>
<td>54 (21.8%)</td>
<td>79 (17.4%)</td>
</tr>
<tr>
<td>HAI-F4</td>
<td>8 (3.2%)</td>
<td>11 (2.4%)</td>
</tr>
</tbody>
</table>
Experience with HBeAg -ve HBV Infection

Clinical Use of Liver Biopsy for the Diagnosis and Management of Inactive and Asymptomatic Hepatitis B Virus Carriers in Bangladesh

Mamun Al-Mahtab,1 Salimur Rahman,1 Sheikh Mohammad Fazle Akbar,2* Mohammad Kamal,3 and Mohammad Sakirul Islam Khan1
1Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
2Department of Medical Sciences, Toshiba General Hospital, Tokyo, Japan
3Department of Pathology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
4Department of Animal Science, Bangladesh Agricultural University, Mymensingh, Bangladesh

Patients with inactive chronic hepatitis B virus (HBV) infection are assumed to be free from liver disease. Accordingly, antiviral drug treatment is not recommended for these patients. However, the extent of liver damage in these patients has not been evaluated fully. The aim of this study was to evaluate the extent of liver damage in patients with inactive HBV. Liver biopsy was conducted in 141 inactive HBV carriers (HBeAnegative, low levels of HBV DNA (<10,000 IU/ml)).

**INTRODUCTION**

Chronic hepatitis B virus (HBV) infection is a global public health problem. An estimated 400 million people worldwide have chronic HBV infection and more than 500,000 die every year because of complications of HBV-related chronic liver diseases [Ganem and Prince, 2004; Perz et al., 2006]. Chronic HBV infection is characterized by a dynamic natural course, which

| TABLE I. Histological Findings for Liver Biopsy Specimens From Patients With Inactive Chronic HBV |
|----------------------------------|----------------------------------|-----------------|-----------------|-----------------|-----------------|
| hepatic activity                 | Number of patients               | HAI-N1 ≤ 3      | 26 (18%)        | 16 (11%)        | 9 (6%)          |
| HAI-N1 4–6                      | 79 (56%)                        |                 |                 |                 |                 |
| HAI-N1 ≥ 7                      | 36 (26%)                        |                 |                 |                 |                 |
| Total                           | 141                             |                 |                 |                 |                 |
| Fibrosis                        |                                 |                 |                 |                 |                 |
| HAI-F0                          | 20 (14%)                        |                 |                 |                 |                 |
| HAI-F1                          | 104 (74%)                       |                 |                 |                 |                 |
| HAI-F3                          | 16 (11%)                        |                 |                 |                 |                 |
| HAI-F4                          | 1 (0.7%)                        |                 |                 |                 |                 |
| Total                           | 141                             |                 |                 |                 |                 |

**Liver Damage in Inactive Chronic HBV Carriers**

<table>
<thead>
<tr>
<th>TABLE II. Clinical Profile of Inactive HBV Carriers With Moderate Necroinflammation and Severe Hepatic Fibrosis</th>
</tr>
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<tbody>
<tr>
<td>Patient</td>
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<tr>
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</tr>
<tr>
<td>1</td>
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<td>2</td>
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<td>8</td>
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<td>9</td>
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<td>10</td>
</tr>
</tbody>
</table>

... in a series of 141 HBeAg -ve CHB patients, 26% had significant hepatic necroinflammation and 11.7% had significant hepatic fibrosis.
Precore/Core Promoter Mutant Hepatitis B Virus Produces More Severe Histologic Liver Disease than Wild Type Hepatitis B Virus

MAMUN-AL-MAHTAB¹, SALIMUR RAHMAN¹, MOBIN KHAN¹, AYUB AL MAMUN¹, MD. KAMAL²

¹Department of Hepatology, ²Department of Pathology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

Introduction: The aim of this study is to compare Knodell and HAI scores in patients with wild type and precore/core promoter mutant CHB to see if there is any difference in severity of liver injury between these two types of HBV. Methods: We did percutaneous liver biopsies of 155 patients. Rather HBeAg -ve may have more severe liver diseases seen in a series of 155 patients.
Implication of High and Low ALT within Normal Range

In a series of 255 CHB patients with normal ALT, 12% had significant hepatic necroinflammation and 13.5% had significant hepatic fibrosis and 5.5% had both.
HBV DNA Level Unrelated to Liver Disease Severity

Viral load speaks little about toll on liver
Mamun-Al Mahtab, Salimur Rahman, Mobin Khan, Md Kamal, Ayub Al Mamun and Md Fazal Karim

Dhaka, Bangladesh

BACKGROUND: Bangladesh is situated in the intermediate prevalence region of hepatitis B virus (HBV). The lifetime risk of acquiring HBV infection in Bangladesh is greater than 40%. It has been estimated that this virus is responsible for 10%-35% cases of acute viral hepatitis, 35.7% cases of fulminant hepatic failure, and 50% of deaths due to liver disease. In the core/core promoter mutant type CHB, in the moderate to high HBV DNA group, 79.5% (35 patients) had minimal to mild chronic hepatitis (HAI-NI 0-8) and 20.5% (9) had moderate to severe chronic hepatitis (HAI-NI 9-18). 93.3% (14) and 6.7% (1) patients with low to moderate HBV DNA load had minimal to mild and moderate to severe chronic hepatitis, respectively.

in a series of 159 CHB patients, the study failed to observe any correlation between serum HBV DNA load and liver histology.
Early termination of immune tolerance state of hepatitis B virus infection explains liver damage

Mamun-Al-Mahtab, Sheikh Mohammad Fazle Akbar, Helal Uddin, Sakirul Islam Khan, Salimur Rahman

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Sheikh Mohammad Fazle Akbar, Department of Medical Science, National Institute of Women's Health, Dhaka 1207, Bangladesh

was observed in 57 (70.4%) patients. PCM was negative in all 8 patients.

CONCLUSION: This study indicates that the current

Table 1 Baseline characteristics of study population

<table>
<thead>
<tr>
<th>Parameters</th>
<th>81</th>
</tr>
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<tbody>
<tr>
<td>Total number of patients</td>
<td>81</td>
</tr>
<tr>
<td>Male</td>
<td>60 (74%)</td>
</tr>
<tr>
<td>Female</td>
<td>21 (26%)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>17.5 ± 2.8</td>
</tr>
<tr>
<td>ALT ≤ 42 (U/L)</td>
<td>52 (65.2%)</td>
</tr>
<tr>
<td>ALT &gt; 42 (U/L)</td>
<td>29 (34.8%)</td>
</tr>
<tr>
<td>DNA ≤ 100,000 (copies/mL)</td>
<td>57 (70.4%)</td>
</tr>
<tr>
<td>DNA &gt; 100,000 (copies/mL)</td>
<td>24 (29.6%)</td>
</tr>
<tr>
<td>Non-significant hepatic necroinflammation</td>
<td>44 (53.8%)</td>
</tr>
<tr>
<td>(HAI-NI ≤ 7)</td>
<td>37 (45.7%)</td>
</tr>
<tr>
<td>Significant hepatic necroinflammation</td>
<td></td>
</tr>
<tr>
<td>(HAI-NI &gt; 7)</td>
<td></td>
</tr>
<tr>
<td>Non-significant hepatic fibrosis (HAI-F &lt; 3)</td>
<td>66 (81%)</td>
</tr>
<tr>
<td>Significant hepatic fibrosis (HAI-F ≥ 3)</td>
<td>15 (18.5%)</td>
</tr>
</tbody>
</table>
| Cirrhosis                                 | 2/15

Young HBV patients of immuno-tolerant age group may have significant liver disease in Bangladesh.
<table>
<thead>
<tr>
<th>Treatment Recommendations</th>
<th>Authors</th>
<th>Journal and Year</th>
</tr>
</thead>
</table>
NIH Consensus Conference
(Analysis of all RCTs in CHB from 1980-2008)

- Final outcome improved: 0 of 25 RCTs
- All intermediate outcomes improved: 0 of 60 RCTs
- Some intermediate outcomes improved: in few RCTs
……. In a series of 50 CHB patients, there was no improvement of QoL at 6 months on Lamivudine.
Predicting HCC Early!

Exploring HBV Genome
Distribution of HBV Genotype in Bangladesh

Mahtab et. al  SAAP (Abstract) 2014
High Prevalence of Mutation at 1654 and 1754 in HCC

Mahtab et. al SAAP (Abstract) 2014
Low Prevalence of Mutation at 1654 and 1754 in ASC

Mutation about 20%

Specific mutation seems to be related to hepato-carcinogenesis

Mahtab et. al SAAP (Abstract) 2014
Predicting HCC Early!

Exploring Human Genome
Discovery and Validation of DNA Hypomethylation Biomarkers for Liver Cancer Using HRM-Specific Probes

Barbara Stefanska¹, Aurelie Bouzelmat¹, Jian Huang², Matthew Suderman¹, Michael Hallett³, Ze-Guang Han², Mamun Al-Mahtab⁵, Sheikh Mohammad Fazle Akbar⁵, Wasif Ali Khan⁶, Rubhana Raqib⁶, Moshe Szyf¹,⁷

¹Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada, ²Shanghai-MOST Key Laboratory for Disease and Health Genomics, Chinese National Human Genome Center at Shanghai, Shanghai, Shanghai, China, ³McGill Centre for Bioinformatics, McGill University, Montreal, Quebec, Canada, ⁴Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Dhaka District, Bangladesh, ⁵Department of Medical Sciences, Toshiba General Hospital, Kanto, Japan, ⁶International Centre for Diarrhoeal Diseases Research, Bangladesh (icddr,b), Dhaka, Dhaka District, Bangladesh, ⁷Sackler Program for Psychobiology and Epigenetics at McGill University, McGill University, Montreal, Quebec, Canada

Abstract

Distinguishing HCC from Normal Tissue

- High resolution melting analysis (HRM) by PCR for detecting differences in DNA methylation
- None of these genes or their methylation state previously linked to HCC
Distinguishing HCC from CHB

MAGEA12

FCRL1

Abstract

Discovery and Validation of DNA Hypomethylation Biomarkers for Liver Cancer Using HRM-Specific Probes

Barbara Stefanska¹, Aurelie Bouzelmat¹, Jian Huang², Matthew Suderman¹, Michael Hallett³, Ze-Guang Han², Mamun Al-Mahtab⁴, Sheikh Mohammad Fazle Akbar⁵, Wasif Ali Khan⁶, Rubhana Raqib⁶, Moshe Szyf¹,⁷*

¹Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada, ²Shanghai-MOST Key Laboratory for Disease and Health Genomics, Chinese National Human Genome Center at Shanghai, Shanghai, Shanghai, China, ³McGill Centre for Bioinformatics, McGill University, Montreal, Quebec, Canada, ⁴Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Dhaka District, Bangladesh, ⁵Department of Medical Sciences, Toshiba General Hospital, Tokyo, Kanto, Japan, ⁶International Centre for Diarrhoeal Diseases Research, Bangladesh (icddr,b), Dhaka, Dhaka District, Bangladesh, ⁷Sackler Program for Psychobiology and Epigenetics at McGill University, McGill University, Montreal, Quebec, Canada

CHB

HCC
IL28B SNP in Predicting HBV-HCC

- HBV- HCC 44; non-HCC chronic HBV infection 42; healthy controls 32
- Single nucleotide polymorphism (SNP) in IL28B gene (rs12979860 C/T) studied
- CC homozygosity
  - Non-HCC chronic HBV infection vs healthy controls (not significant)
  - Healthy control (70%) vs HBV-HCC (45.5%)
  - Non-HCC chronic HBV infection (69%) vs HBV-HCC (45.5%)
- Carriers of minor T allele in rs12979860 had higher risk of HCC
- Results suggest that IL28B rs12979860 C/T polymorphism might affect susceptibility to HBV-HCC

Islam, (Mahtab) et al World J Hepatol 2013 (in press)
Development of Novel Anti-HBV Therapy
Hepatitis B Management Guideline for Bangladesh

South Asian Guideline Being Planned

Rahman, (Mahtab) et. al Bangladesh Liver J 2009
Lamivudine plus HBV-Vaccine in Adult CHB

Brief Report

Combination Therapy with Antiviral Drugs and Hepatitis B Vaccine in Incidentally-Detected and Asymptomatic Chronic Hepatitis Virus B Carriers at Bangladesh


Abstract

Asymptomatic chronic hepatitis B virus (HBV) carriers are at risk of developing complications of liver disease, but these patients are not recommended for treatment with antiviral drugs. In fact, antiviral drugs are ineffective in these patients in the immune tolerance phase, when they have inadequate levels of host immunity. We postulated that combination therapy of an immune modulator and antiviral drugs may have potential to help these patients. Twenty-five patients with incidentally-detected asymptomatic chronic HBV were immunized with hepatitis B vaccine (0.5ml of hepatitis B vaccine intramuscularly) three times (0, 1, 2, 6, and 12th).

![Graph showing combination therapy in asymptomatic chronic HBV](image)

**FIG. 1.** Protocol of the combination therapy used in incidentally-detected asymptomatic chronic hepatitis B virus (HBV)-infected patients. All patients were given lamivudine at a dose of 6mg daily for 24 weeks. Combination drug of hepatitis B vaccine was administered intermittently at 0, 1, 2, 6, and 12th. Viral loads were monitored periodically in all patients via total blood exams and assessments of liver and kidney function. Assessment of HBV-related pathological and immunological markers were done at months 6, 7, and 12.

**FIG. 3.** Indicates that HBV-DNA was initially high, after combination therapy and HBV-DNA became undetectable to 15th/25th of patients 3/6.

Lamivudine plus Interferon in Paediatric CHB

INTERNATIONAL JOURNAL OF IMMUNOPATHOLOGY AND PHARMACOLOGY

LETTER TO THE EDITOR

COMBINATION THERAPY OF LAMIVUDINE AND INTERFERON-ALPHA IN PEDIATRIC PATIENTS WITH CHRONIC HEPATITIS B IN BANGLADESH: A SAFE AND EFFECTIVE THERAPEUTIC APPROACH FOR PEDIATRIC CHB PATIENTS IN DEVELOPING COUNTRIES

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1 Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh; 2 Department of Medical Sciences, Toshifa General Hospital, Tokyo, Japan; 3 Department of Animal Science, Bangladesh Agricultural University, Mymensingh, Bangladesh; 4 Viral Hepatitis Foundation, Dhaka, Bangladesh; 5 Department of Hepatology, Dhaka Medical College, Bangladesh

Received July 20, 2009 - Accepted April 20, 2010

Hepatitis B virus (HBV) is mainly transmitted during birth or perinatal period, however, treatment is not usually recommended for pediatric patients with chronic hepatitis B (CHB). Twelve pediatric patients with CHB in Bangladesh were treated with both lamivudine and interferon. Lamivudine was given at a dose of 3mg daily for 12 months. Two months after commencement of lamivudine therapy,
New Therapeutic Option for HBV

- HBsAg: P. pastoris-derived recombinant HBsAg
- HBcAg: E. coli-derived HBcAg
- HBsAg + HBcAg: Aggregates of 20-30 nm

Center for Genetic Engineering & Biotechnology (CIGB), Cuba
Nasal device developed in Switzerland
Strong and multi-antigen specific immunity by hepatitis B core antigen (HBcAg)-based vaccines in a murine model of chronic hepatitis B: HBcAg is a candidate for a therapeutic vaccine against hepatitis B virus

Sheikh Mohammad Fazle Akbar a,*, Shiyi Chen b, Mamun Al-Mahtab c, Masanori Abe b, Yoichi Hiasa b, Morikazu Onji b

a Department of Medical Sciences, Toshiba General Hospital, Higashi Oi 6-3-22, Shinagawa, Tokyo 140-8522, Japan
b Department of Gastroenterology and Metabolism, Ehime University Graduate School of Medicine, Ehime, Toon City, Ehime 791-0295, Japan
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A R T I C L E   I N F O
Article history:
Received 11 April 2012
Revised 24 July 2012
Accepted 24 July 2012
Available online 1 August 2012

K e y w o r d s:
Chronic hepatitis B

A B S T R A C T
Experimental evidence suggests that hepatitis B core antigen (HBcAg)-specific cytotoxic T lymphocytes (CTL) are essential for the control of hepatitis B virus (HBV) replication and prevention of liver damage in patients with chronic hepatitis B (CHB). However, most immune therapeutic approaches in CHB patients have been accomplished with hepatitis B surface antigen (HBsAg)-based prophylactic vaccines with unsatisfactory clinical outcomes. In this study, we prepared HBsAg-pulsed dendritic cells (DC) and HBcAg-pulsed DC by culturing spleen DC from HBV transgenic mice (HBV TM) and evaluated the immunomodulatory capabilities of these antigens, which may serve as a better therapy for CHB. The kinetics of HBsAg-specific antibody levels against HBsAg (anti-HBs) quantification of HBcAg, and HBsAg-specific
Hepatitis B Transgenic Mice (TM)

HBsAg in sera

HBV DNA in the liver

No Anti-HBs in sera

HBsAg/HBcAg Vaccine in Healthy Volunteers

Betancourt et al.

Phase I clinical trial in healthy adults of a nasal vaccine candidate containing recombinant hepatitis B surface and core antigen

Phase I Clinical Trial in Bangladesh

Safety: Satisfactory
Efficacy: HBV DNA negativity and ALT normalized and maintained in 50%
Mechanism: HBsAg & HBcAg-specific immune induction and antigen-specific activation of DC
Phase III Clinical Trial in Bangladesh

- **Number**: 151
- **Diagnosis**: Chronic hepatitis B
- **Age**: 18-52 yrs
- **HBeAg (+)**: 20%
- **HBeAg (-)**: 80%
- **ALT**: > ULN (HBeAg-negative)  
  > 1.5 x ULN (HBeAg-positive)
- **HBV DNA**: > 1 x 10^3 copies/ml (HBeAg-negative)  
  > 1 x 10^4 copies/ml (HBeAg-positive)
  (Randomly selected in two groups)

Patients receiving HBsAg/HBcAg vaccine: 75 patients
Patients receiving Peg-IFN: 76 patients

HBsAg/HBcAg vaccine and pegylated interferon: Centre for Genetic and Biotechnology, Havana, Cuba

Ethical approval from: BSMMU & BMRC, Approved by: MoFA, DGDA; Registered with: ClinicalTrials.gov
GCP certification by: Cuban Drug Administration

Mahtab et al. Hepatology (Suppl) 2013
HBV DNA in Patients on HBsAg/HBcAg Vaccine

NASVAC patients: EOT & 24 weeks follow-up

Viral load < 250 copies/mL

63.9%  62.5%

Mahtab et al.  Hepatology (Suppl) 2013
HBV DNA in Patients on Pegylated IFN

PegIFN patients: EOT & 24 weeks follow-up

65% 33%

Viral load <250 copies/ml

Mahtab et al. Hepatology (Suppl) 2013
Kinetics of qHBsAg after HBsAg plus HBcAg-Based Immune Therapy Vs Peg-IFN

Mahtab et al. Hepatology (Suppl) 2014
HCV in Bangladesh
Prevalence and Risk Factors of Asymptomatic Hepatitis C Virus Infection in Bangladesh

Sample size: 1028 apparently healthy subjects
Method of study: Questionnaire
Study Place: Savar, Dhaka
Prevalence: 0.8% (1% of world’s HCV population)
<table>
<thead>
<tr>
<th>Prevalence (%)</th>
<th>Location</th>
<th>Authors</th>
<th>Source</th>
</tr>
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<tbody>
<tr>
<td>5% in general population</td>
<td>Akbar et al.</td>
<td>Hepatol Res 1997</td>
<td></td>
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<tr>
<td>0.2% in Dhaka slum</td>
<td>Ashraf et al.</td>
<td>MC Infect Dis. 2010</td>
<td></td>
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<tr>
<td>6.25% in Mymensingh</td>
<td>Rudra et al.</td>
<td>Mymensingh Med J. 2011</td>
<td></td>
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<tr>
<td>0.04% in Khulna</td>
<td>Rudra et al.</td>
<td>Mymensingh Med J 2010</td>
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<tr>
<td>0.09% in Bangladeshis in Spain</td>
<td>Aliberch et al.</td>
<td>Gac Sanitt 2010</td>
<td></td>
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<tr>
<td>0.6% in Bangladeshis in UK</td>
<td>Uddin et al.</td>
<td>J Viral Hepat. 2010</td>
<td></td>
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<tr>
<td>24.8% in IV drug abusers</td>
<td>Shirin et al.</td>
<td>J Health Popul Nutr. 2000</td>
<td></td>
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<tr>
<td>2% in thalassaemia</td>
<td>Chakrabarty et. al.</td>
<td>Mymensingh Med J. 2014</td>
<td></td>
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</tbody>
</table>
HCV Induced Disease Burden

Mahtab et. al. Indian J Gastroenterol (Suppl) 2007
Afroz et al. Hepatol Int (Suppl) 2007
Mahtab et. al. Hepatol Int (Suppl) 2009
HCV Genotypes in Bangladesh

- Genotype 3: 89.20%
- Genotype 1: 8.10%
- Mixed Genotype: 2.70%

n 60

Mahtab et. al J. Gastro Hepatol. (Suppl) 2008
HCV Treatment Response in Bangladesh

ETR in 3: 80%
ETR in 1: 100%
ETR in Mixed: 100%
Side Effect: 2.70%
Lost on FU: 5.40%

n 60

Mahtab et. al J. Gastro Hepatol. (Suppl) 2008
Bangladesh Wins Freedom!

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But Victory Came at a Very High Price!

A Price that We All Paid!!
Not the Bangladesh We Dream of!

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“Bangladesh has left India behind in all social indicators” Amartya Sen

‘G.L. Mehta Memorial Lecture’ at the Indian Institute of Technology, Mumbai

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I declare that I have no conflicts of interest.
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