Prevention of recurrent hepatitis B after liver transplantation

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China
300-400 million chronic HBV
600,000/year died from chronic HBV/liver cancer
LIVER TRANSPLANTATION FOR HBV

From HBIG to combination of Lamivudine + HBIG

- No prophylaxis
- IV HBIG
  - Samuel, NEJM 1993
- High dose IV HBIG
  - Terrault, Hepatology 1996
- High dose IV HBIG + LAM
  - Markowitz, Hepatology 1998
LIVER TRANSPLANTATION FOR HBV
Combination of Lamivudine + HBIG prophylaxis

<table>
<thead>
<tr>
<th>Author</th>
<th>year</th>
<th>number</th>
<th>HBV recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markowitz</td>
<td>1998</td>
<td>14</td>
<td>0%</td>
</tr>
<tr>
<td>Han</td>
<td>2000</td>
<td>59</td>
<td>0%</td>
</tr>
<tr>
<td>Yao</td>
<td>1999</td>
<td>10</td>
<td>10%</td>
</tr>
<tr>
<td>Yoshida</td>
<td>1999</td>
<td>7</td>
<td>0%</td>
</tr>
<tr>
<td>Angus</td>
<td>2000</td>
<td>32</td>
<td>3%</td>
</tr>
<tr>
<td>Morzano</td>
<td>2001</td>
<td>26</td>
<td>4%</td>
</tr>
<tr>
<td>Rosenau</td>
<td>2001</td>
<td>21</td>
<td>9.5%</td>
</tr>
</tbody>
</table>
LIVER TRANSPLANTATION FOR HBV

HBIG Prophylaxis

- Parenteral administration
  - Inconvenience of clinic/hospital visit
  - Painful

- Toxicity/Reactions

- High cost
  - Clinic/hospital visit monthly
  - Monitoring of anti-HBs titer
  - For high dose IV HBIG
    - US$ 75,000 – 120,000 1st year
    - US$ 60,000 each year long-term
LIVER TRANSPLANTATION FOR HBV
Strategies to improve HBV prophylaxis: western perspective

乙型肝炎免疫球蛋白 HBIG Dose Reduction
Han et al, Liver Transplantation 2003
Gane E et al, Gastroenterology 2007

HBIG Dose Withdrawal
Buti M et al, J Hepatol 2003
Buti M et al, Transplantation 2007
Angus PW et al, Hepatology 2008

HBIG Dose Avoidance
Prophylactic Strategies for Hepatitis B Patients Undergoing Liver Transplant: A Cost-Effectiveness Analysis

Yock Young Dan,¹ Chun Tao Wai,¹ Khay Guan Yeoh,¹ and Seng Gee Lim¹
Department of Gastroenterology, National University Hospital, Singapore

US$50,000/QALY

IV HBIG target [anti-HBs] >500
Han et al, 2000

IV HBIG target [anti-HBs] >100
Shouval et al, 2000

IV HBIG stop in low-risk
Lok et al, 2002

IV then IM HBIG
Han et al, 2003

low dose IM HBIG
Gane et al, 2007

Dan et al Liver Transplantation 2006
Cost-effectiveness of HBIG

Prophylactic Strategies for Hepatitis B Patients Undergoing Liver Transplant: A Cost-Effectiveness Analysis

Yock Young Dan,' Chun Tao Wai,3 Khay Guan Yeoh,1 and Seng Gee Lim1
Department of Gastroenterology, National University Hospital, Singapore

Dan et al Liver Transplantation 2006
Liver transplantation: Hong Kong

Disease Indications (1991-2018) n=1368

- HBV: 60.4%
- Hepatocellular carcinoma: 22.3%
- Biliary atresia: 8.3%
- PBC: 3.4%
- Wilson: 2.1%
- Retransplant: 4.1%
- Polycystic disease: 0.7%
- Others: 9.1%
- FHF: 6.1%
- HCV: 5.7%
LIVER TRANSPLANTATION

HBV as Disease Indication

![Bar chart showing percentage of HBV among liver transplant recipients in Hong Kong, mainland China, Taiwan, and Korea.](chart.png)
Asia
USA
Annual no. of OLT 1,000 1,000
Proportion of HBV 70% 5%
Annual no. 700 50

OLT 原位肝移植 for HBV
Annual HBIG 乙型肝炎免疫球蛋白 cost (US$) 4,200K 300K

Assuming cost of low dose IM HBIG per patient = US$ 6,000/year

LIVER TRANSPLANTATION FOR HBV
Annual Cost of HBIG

Annual Cost (US$‘000)

Year
USA Asia

US$ 42M
US$ 3M
LIVER TRANSPLANTATION FOR HBV

Strategies to improve HBV 乙型肝炎免疫球蛋白prophylaxis

**Western perspective**

**HBIG Dose Reduction**
Han et al, Liver Transplantation 2003
Gane E et al, Gastroenterology 2007

**HBIG Dose Withdrawal**
Buti M et al, J Hepatol 2003
Buti M et al, Transplantation 2007
Angus PW et al, Hepatology 2008

**QMH perspective**

**HBIG Dose Avoidance**
Lamivudine monoprophylaxis
Lo et al, Ann Surg 2001

**More Effective Anti-viral Agents**

**HBIG Dose Avoidance**

**Restoration of Host Immunity**
Adoptive Immunity Transfer
Active Immunization
LIVER TRANSPLANTATION FOR HBV

HBIG Avoidance: Nucleoside analogue prophylaxis

• From 1996 to 2007
  – Lamivudine 100mg daily
  – Add-on Adefovir for mutants with viral breakthrough

• From 2007 onwards
  – Entecavir 0.5mg daily
  – Combination therapy for mutants with viral breakthrough

• HBIG not used before, during, or after transplantation
Median HBV DNA Decline with Current Antiviral Therapies

**HBeAg-positive**

- ADV: -3.5
- LAM: -5.5
- TNV: -6.2
- TBV: -6.4
- ETV: -6.9

**HBeAg-negative**

- ADV: -3.9
- LAM: -4.7
- TNV: -4.6
- TBV: -5.2
- ETV: -5

Non head-to-head studies
Antiviral Resistance in Chronic Hepatitis B

Entecavir Monotherapy Is Effective in Suppressing Hepatitis B Virus After Liver Transplantation

JAMES FUNG,* CINDY CHEUNG,‡ SEE–CHING CHAN,‡,§ MAN–FUNG YUEN,*§ KENNETH S. H. CHOK,§ WILLIAM SHARR,§ WING–CHIU DAI,§ ALBERT C. Y. CHAN,§ TAN–TO CHEUNG,§ SIMON TSANG,§ BANNY LAM,§ CHING–LUNG LAI,*§ and CHUNG–MAU LO‡,§

Departments of *Medicine and §Surgery, Queen Mary Hospital, and ‡State Key Laboratory for Liver Research, The University of Hong Kong, Pokfulam, Hong Kong SAR, China

November 2007 to December 2009
80 patients
Median follow up 26 months

Median time to HBsAg loss = 1 (0 to 16) months

1 of 80 positive for HBVDNA (217 copies/mL) at last follow up

Graft survival 94% at 30 months

5 deaths
Sepsis 3
Myocardial infarction 1
PCP 1

Cumulative Survival

Follow-up (Months)

Log HBV DNA (copies/mL)

Time of transplant
Month 1-3 Month 6 Month 12 Month 24

Lower limit of detection

Number of patients at risk
Overall group 80
9 3 0
Long-Term Outcomes of Entecavir Monotherapy for Chronic Hepatitis B After Liver Transplantation: Results up to 8 Years

(Hepatology 2017;66:1036-1044)

James Fung 1,3 Tiffany Wong,1,4 Kenneth Chok 1,4 Albert Chan,1,4 Tan-To Cheung,1,4 Jeff Wing-Chiu Dai,1,4 Sui-lung Sin,1,4 Ka-Wing Ma,1,4 Kelvin Ng,1,4 Kevin Tak-Pan Ng,4 Wai-Kay Seto 1,2,3 Ching-Lung Lai,2,3
Man-Fung Yuen 1,2,3 and Chung-Mau Lo 1,3,4

From the 1Liver Transplant Center, Queen Mary Hospital, Hong Kong; 2Division of Gastroenterology and Hepatology, Department of Medicine, 3State Key Laboratory for Liver Research, and 4Division of Liver Transplantation, Department of Surgery, The University of Hong Kong, Hong Kong.

265 hepatitis B Patients on entecavir monotherapy after liver transplantation

7 early post-operative deaths
- 6 sepsis/multi-organ failure
- 1 cardiac arrest
2 early re-transplantation
- 1 hepatic artery thrombosis
- 1 primary non-function

Graft survival 86% at 5 years and 85% at 9 years

37 deaths
None due to HBV
Long-Term Outcomes of Entecavir Monotherapy for Chronic Hepatitis B After Liver Transplantation: Results up to 8 Years

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Nov 2007 to Dec 2014
265 patients
Median follow up 59 months
Long-Term Outcomes of Entecavir Monotherapy for Chronic Hepatitis B After Liver Transplantation: Results up to 8 Years

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- Nov 2007 to Dec 2014
- 265 patients
- Median follow up 59 months

![Graph showing liver stiffness (kPa) with different HBsAg status after liver transplantation.](image)
Outcomes Including Liver Histology After Liver Transplantation for Chronic Hepatitis B Using Oral Antiviral Therapy Alone


James Fung, Regina Lo, See-Ching Chan, Kenneth Chok, Tiffany Wong, William Sharr, Tan-To Cheung, Albert C. Y. Chan, Wing-Chiu Dai, Sui-Ling Sin, Irene Ng, Ching-Lung Lai, Man-Fung Yuen, and Chung-Mau Lo

1 Liver Transplant Center, Queen Mary Hospital, Departments of 2 Medicine, 3 Pathology, 4 Surgery, and 5 State Key Laboratory for Liver Research, The University of Hong Kong, Hong Kong

2003-2012: 435 patients
36 serum HBsAg+, HBVDNA- no histologic evidence of HBV recurrence

TABLE 4. Characteristics of Patients on Entecavir Monotherapy With Positive HBsAg in Serum

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>HBV DNA</th>
<th>HBsAg Stain</th>
<th>Histological Diagnosis</th>
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<tbody>
<tr>
<td>1</td>
<td>Negative</td>
<td>Negative</td>
<td>LDO</td>
</tr>
<tr>
<td>2</td>
<td>Negative</td>
<td>Negative</td>
<td>NSC</td>
</tr>
<tr>
<td>3</td>
<td>Negative</td>
<td>Negative</td>
<td>Cholestasis</td>
</tr>
<tr>
<td>4</td>
<td>Negative</td>
<td>Negative</td>
<td>NSC</td>
</tr>
<tr>
<td>5</td>
<td>Negative</td>
<td>Negative</td>
<td>NSC</td>
</tr>
<tr>
<td>6</td>
<td>Negative</td>
<td>Negative</td>
<td>NSC</td>
</tr>
<tr>
<td>7</td>
<td>Negative</td>
<td>Negative</td>
<td>LDO and ACR</td>
</tr>
<tr>
<td>8</td>
<td>Negative</td>
<td>Negative</td>
<td>NSC</td>
</tr>
<tr>
<td>9</td>
<td>Negative</td>
<td>Negative</td>
<td>NSC</td>
</tr>
</tbody>
</table>
Oral Nucleos(t)ide Analogs Alone After Liver Transplantation in Chronic Hepatitis B With Preexisting rt204 Mutation

James Fung, MD,1,2,3 Tiffany Wong, MBBS,1,4 Kenneth Chok, MS,1,4 Albert Chan, MS,1,4 Sui-ling Sin, MBBS,1,4 Tan-to Cheung, MS,1,4 Wing-Chiu Dai, MBBS,1,4 Kelvin Ng, MS,1,4 Kevin Ng, PhD,4 Kwan Man, PhD,3,4 Wai-kay Seto, MD,2,3 Ching-Lung Lai, MD,2,3 Man-Fung Yuen, MD, PhD,2,3 and Chung-Mau Lo, MS1,3,4

Jan 2003 to Dec 2014
57 patients
Median follow up 73 months

5 deaths
Recurrent HCC 4
Sepsis 1

87%
Oral Nucleos(t)ide Analogs Alone After Liver Transplantation in Chronic Hepatitis B With Preexisting rt204 Mutation

James Fung, MD, Tiffany Wong, MBBS, Kenneth Chok, MS, Albert Chan, MS, Sui-ling Sin, MBBS, Tan-to Cheung, MS, Wing-Chiu Dai, MBBS, Kelvin Ng, MS, Kevin Ng, PhD, Kwan Man, PhD, and Chung-Mau Lo, MS

Transplantation 2017;101: 2391–2398

Graphs showing the percentage of negative HBsAg and undetectable HBV DNA over time after liver transplantation, with median liver stiffness values for different groups.
LIVER TRANSPLANTATION FOR HBV

Paradigm Shift in Prophylaxis

1990's

HBIG

High dose IV

Low dose IV

Low dose IM

HBIG Withdrawal

HBIG Free

1990's

Oral NAs

Lamivudine

Adefovir

Entecavir & Tenofovir

2010's

Higher potency. Lower resistance

Decreasing HBIG use

Withdrawal

HBIG Free

Lamivudine

Adefovir

Entecavir & Tenofovir

Higher potency. Lower resistance
LIVER TRANSPLANTATION FOR HBV

Strategies to improve HBV prophylaxis: 玛丽医院 QMH perspective

- **HBIG Dose Avoidance**
  - Lamivudine monoprophylaxis

- **More Effective Anti-viral Agents**
  - Fung et al, Gastroenterology 2011
  - Fung et al, Hepatology 2017
  - Fung et al Transplantation 2017

- **Restoration of Host Immunity**
  - Adoptive Immunity Transfer
  - Active Immunization
21 of 50 patients with chronic HBV developed anti-HBs after liver transplantation.

**Time to develop:** 8 (1-43) days

**Time to disappear:** 207 (24-414) days

<table>
<thead>
<tr>
<th>Peak titer</th>
<th>no.</th>
<th>median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>10</td>
<td>37 (12-84)</td>
</tr>
<tr>
<td>100-1,000</td>
<td>5</td>
<td>252 (101-281)</td>
</tr>
<tr>
<td>&gt;1,000</td>
<td>6</td>
<td>8,081 (1,000-121,000)</td>
</tr>
</tbody>
</table>

Lo et al Hepatology 2003
<table>
<thead>
<tr>
<th>Donor</th>
<th>anti-HBc</th>
<th>anti-HBs</th>
<th>anti-HBs production</th>
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<tbody>
<tr>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>12</td>
</tr>
<tr>
<td>positive</td>
<td>negative</td>
<td>negative</td>
<td>7</td>
</tr>
<tr>
<td>negative</td>
<td>positive</td>
<td>positive</td>
<td>3</td>
</tr>
<tr>
<td>positive</td>
<td>positive</td>
<td>positive</td>
<td>7</td>
</tr>
</tbody>
</table>

**Odd ratio**: 18.9  
**95% CI**: 3.2-112.4  
**P-value**: 0.001

Lo et al Hepatology 2003
LIVER TRANSPLANTATION

Donor Migratory Lymphocytes

• Immunologic disease
  – Graft-versus-host disease 移植物抗宿主病
  – Immune-haemolytic anemia 免疫溶血性贫血
  – Idiopathic thrombocytopenic purpura 特发性血小板减少性紫癜

• Peanut allergy 花生过敏

• Adoptive immunity 继承性免疫
  – Anti-HBs production
ADOPTIVE HBV IMMUNITY TRANSFER

HBV-specific 淋巴细胞 Lymphocytes in Liver Graft

Anti-HBs secreting B cell 2.7/10E6 lymphocytes

HBsAg specific IFN-secreting T cell 4.8/10E6 lymphocytes

HBcAg specific IFN-secreting T cell 4.8/10E6 lymphocytes

ELISPOT assay 酶联斑点试验

Luo et al Liver Transplantation 2006
ADOPTIVE HBV IMMUNITY TRANSFER

HBV-specific Lymphocytes in Liver Graft

Anti-HBs-secreting B cells

<table>
<thead>
<tr>
<th>Group</th>
<th>Anti-HBs</th>
<th>Anti-HBc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Group 2</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Group 3</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Group 4</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Luo et al Liver Transplantation 2006
ADOPTIVE HBV IMMUNITY TRANSFER

HBV-specific Lymphocytes in Liver Graft

HBsAg-specific T cells

\[ P < 0.001 \]

HBcAg-specific T cells

\[ P = 0.082 \]

Anti-HBs-secreting B cells

\[ P = 0.088 \]

Luo et al Liver Transplantation 2006
LIVER TRANSPLANTATION FOR HBV

Active Immunization- 2nd generation vaccine

52 patients on lamivudine prophylaxis 412 (370-2040) days post-OLT

Response rate 7.7%

Lo et al J Hepatology 2005
LIVER TRANSPLANTATION FOR HBV

Active Immunization - Pre-S containing Vaccine

20 patients on lamivudine prophylaxis 570 (379-2160) days post-OLT

Response rate 50%

Lo et al Am J Transplantation 2007
LIVER TRANSPLANTATION FOR HBV

Booster Vaccination: single dose pre-\textit{S} vaccine

- 86 patients
- Previous responder to vaccination: n = 5
  - Responders: 5/5 (100%)
- Spontaneous anti-HBs seroconversion: n = 81
  - Responders: 16/81 (20%)
Entecavir Monotherapy

HBIG Dose Reduction

HBIG Dose Withdrawal

High Dose IV HBIG

Lamivudine Monotherapy

HBIG+Lam

Restoration of host immunity
Drug-free prophylaxis