Antiviral therapy of special populations infected with HBV

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Special populations infected with HBV

- Patients of HBV-related decompensated cirrhosis, liver failure and hepatocellular carcinoma.

- Patients in particular age or physiological stage: children patients and pregnant patients.

- Patients combined with other diseases: combined with other viral infections, renal diseases, autoimmune thyroid dysfunctions and patients needing immunosuppressive agents or cytotoxic therapies.
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Patients of HBV-related decompensated cirrhosis

- Definitions: Child-Pugh B/C grade of liver cirrhosis, with complications of hepatic encephalopathy, ascites or variceal bleeding etc.

- Antiviral indications: Generally recommend anti-viral treatment when HBV DNA is detectable, some experts recommend appropriate antiviral therapy as long as HBsAg is positive.


- Drugs: NAs: Preferred ETV and TDF, or LAM / LdT + ADV combination therapy.
Both ETV and TDF can improve virology and liver function of decompensated patients.

**Table 6. Efficacy Results at Week 48**

<table>
<thead>
<tr>
<th></th>
<th>TDF (N=45)</th>
<th>FTC/TDF (N=45)</th>
<th>ETV (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBV DNA &lt; 400 copies/mL</strong></td>
<td>31/44 (70.5%)</td>
<td>36/41 (87.8%)</td>
<td>16/22 (72.7%)</td>
</tr>
<tr>
<td>(69 IU/mL) n/N (%)†</td>
<td>57.0%, 83.9%</td>
<td>77.8%, 97.8%</td>
<td>54.1%, 91.3%</td>
</tr>
<tr>
<td><strong>95% confidence interval</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR) change from baseline in HBV DNA (log_{10} copies/mL)*,‡</td>
<td>-3.11 (-4.1, -2.4)</td>
<td>-3.92 (-5.2, -2.2)</td>
<td>-3.40 (-5.0, -1.3)</td>
</tr>
<tr>
<td><strong>Normal ALT§ n/N (%)†</strong></td>
<td>25/44 (56.8%)</td>
<td>31/41 (75.6%)</td>
<td>12/22 (54.5%)</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>42.2%, 71.5%</td>
<td>62.5%, 88.8%</td>
<td>33.7%, 75.4%</td>
</tr>
<tr>
<td>Normalized ALT§ n/N (%)†</td>
<td>12/26 (46.2%)</td>
<td>16/25 (64.0%)</td>
<td>7/17 (41.2%)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>27.0%, 65.3%</td>
<td>45.2%, 82.8%</td>
<td>17.8%, 64.6%</td>
</tr>
<tr>
<td>Median (IQR) change from baseline in serum ALT (U/L)‡</td>
<td>-7.0 (-42.0, 1.0)</td>
<td>-16.5 (-64.5, -2.5)</td>
<td>-25.5 (-44.5, -5.5)</td>
</tr>
<tr>
<td><strong>CTP Score† ≥ 2 point decrease</strong> (n/N; %)</td>
<td>7/27 (25.9%)</td>
<td>12/25 (48.0%)</td>
<td>5/12 (41.7%)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>9.4%, 42.5%</td>
<td>28.4%, 67.6%</td>
<td>13.8%, 69.6%</td>
</tr>
<tr>
<td>CTP Score† ≥ 2 point increase (n/N; %)</td>
<td>0/43</td>
<td>1/38 (2.6%)</td>
<td>0/22</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.0%, 7.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR) change from baseline in MELD score‡</td>
<td>-2.0 (-12, 3)</td>
<td>-2.0 (-18, 4)</td>
<td>-2.0 (-10, 1)</td>
</tr>
<tr>
<td><strong>HBeAg loss,¶ n/N (%)†</strong></td>
<td>3/14 (21.4%)</td>
<td>4/15 (26.7%)</td>
<td>0/7</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>(0.0%, 42.9%)</td>
<td>(4.3%, 49.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>HBeAg seroconversion,¶ n/N (%)†</strong></td>
<td>3/14 (21.4%)</td>
<td>2/15 (13.3%)</td>
<td>0/7</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>(0.0%, 42.9%)</td>
<td>(0.0%, 30.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>HBV recurrence after liver transplantation</strong></td>
<td>0/2</td>
<td>0/4</td>
<td>–</td>
</tr>
</tbody>
</table>
ETV can reduce the incidence of HCC and case rate of cirrhosis patients

Wong GH, Hepatology, 2013
A total of seven randomized controlled study, in which 206 cases are ETV treatment group, 205 cases are LAM + ADV group;

Treated for 48 weeks;

HBV DNA negative rate, ALT normalization rate, HBeAg seroconversion rate and seroconversion rate of two groups are similar;

Improvement of Child-Pugh score of ETV group was better than LAM + ADV group (P < .00001);

Renal damage probability of ETV group was lower than LAM + ADV group (P = .04).
Treatment of acute-on-chronic liver failure caused by HBV reactivation

2015APASL

- Nas should be used immediately to begin treatment. [A1]
- If there is severe liver failure, liver transplantation should be considered. [MELD>30] [B1]
- If HBV DNA reduced 2Log within two weeks, the effect is good, or liver transplantation should be considered. [B1]
NUCs can reduce the rate of tumor recurrence and mortality after HCC surgical resection

- A study from Taiwan included 4051 cases of HCC patients not applied and 518 cases applied NUCs for antiviral therapy, mortality and tumor recurrence of 6-year follow-up of two groups were compared.

Wu C, JAMA, 2012
ETV used as anti-viral therapy for HBV-related liver cancer patients

Anti-viral therapy can reduce the rate of tumor recurrence of HCC patients after partial hepatectomy.

Anti-viral therapy can reduce the mortality rate of HCC patients after partial hepatectomy.

Wu CY, et al. JAMA 2012
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## Existing drugs for children CHB treatment

<table>
<thead>
<tr>
<th>药物</th>
<th>批准应用年龄</th>
<th>剂量</th>
<th>疗程</th>
<th>优势</th>
<th>劣势</th>
</tr>
</thead>
<tbody>
<tr>
<td>干扰素α</td>
<td>≥12个月</td>
<td>500万-1000万单位/m² 皮下注射每周三次</td>
<td>6个月</td>
<td>• 无耐药性；• 可用于低龄儿童；• 疗程短</td>
<td>• 副作用；• 非口服给药；• 不适于失代偿期肝硬化或器官移植人群</td>
</tr>
<tr>
<td>拉米夫定</td>
<td>≥3岁</td>
<td>3 mg/kg/d（最大剂量100 mg/d）口服</td>
<td>≥1年</td>
<td>• 副作用少；• 口服给药；• 可用于孕晚期妇女</td>
<td>• 高耐药发生率（随应用时间延长耐药率增加）</td>
</tr>
<tr>
<td>阿德福韦酯</td>
<td>≥12岁</td>
<td>10 mg/d 口服</td>
<td>≥1年</td>
<td>• 对拉米夫定耐药患者部分有效；• 口服给药</td>
<td>• 不能用于&lt;12岁的患儿；• 高耐药发生率（随应用时间延长耐药率增加）</td>
</tr>
<tr>
<td>恩替卡韦</td>
<td>≥16岁及II期试验（2-17岁）</td>
<td>0.5 mg/d 口服（1 mg/d 拉米夫定耐药者）</td>
<td>≥1年</td>
<td>• 低耐药发生率；• 口服给药</td>
<td>• 不能用于&lt;16岁的患儿</td>
</tr>
<tr>
<td>替诺福韦</td>
<td>≥12岁</td>
<td>300 mg/d 口服</td>
<td>≥1年</td>
<td>• 高治疗应答率；• 未见耐药发生；• 副作用少；• 口服给药；• 可用于孕晚期妇女</td>
<td>• 不能用于&lt;12岁的患儿；• 降低儿童骨密度</td>
</tr>
<tr>
<td>聚乙二醇干扰素α</td>
<td>II期（2-18岁）</td>
<td>180 μg/w</td>
<td>6个月</td>
<td>• 无耐药突变；• 每周1次给药；• 疗程短</td>
<td>• 副作用；• 非口服给药；• 不适于失代偿期肝硬化或器官移植人群</td>
</tr>
<tr>
<td>替比夫定</td>
<td>Ⅰ期（2-18岁）</td>
<td>600 mg/d 口服</td>
<td>≥1年</td>
<td>• 副作用少；• 口服给药；• 可用于孕晚期妇女</td>
<td>• 高耐药发生率</td>
</tr>
</tbody>
</table>
ETV used as antiviral therapy for children CHB patients

- **Subjects:**
  Prospective follow-up study of ETV treatment for children CHB patients;
  30 cases of children CHB patients aged 5-17;
  Previously treated by IFNα / LAM / ADV;

- **Treatment:** ETV 0.5 mg (LAM-N) / 1.0 mg (LAM-R) qd;

- **The primary outcome:** Decrease of HBV DNA load and ALT after 24 weeks of treatment.

ETV used as antiviral therapy for children CHB patients

22 cases of HBeAg positive children CHB patients

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>After 24 weeks of treatment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Median</td>
<td>Mean±SD</td>
</tr>
<tr>
<td>Serum HBV DNA (IU/mL)</td>
<td>80514591±97425806</td>
<td>77500000</td>
<td>91654±253703</td>
</tr>
<tr>
<td></td>
<td>Min 1000</td>
<td></td>
<td>Min 0.0000</td>
</tr>
<tr>
<td></td>
<td>Max 410000000</td>
<td></td>
<td>Max 1100000</td>
</tr>
<tr>
<td>ALT activity (U/L)</td>
<td>214±326</td>
<td>75</td>
<td>38.59±19.2</td>
</tr>
</tbody>
</table>

8 cases of HBeAg negative children CHB patients

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>After 24 weeks of treatment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Median</td>
<td>Mean±SD</td>
</tr>
<tr>
<td>Serum HBV DNA (IU/mL)</td>
<td>35491±29886</td>
<td>25000</td>
<td>69±51</td>
</tr>
<tr>
<td></td>
<td>Min 6840</td>
<td></td>
<td>Min 50</td>
</tr>
<tr>
<td></td>
<td>Max 96200</td>
<td></td>
<td>Max 184</td>
</tr>
<tr>
<td>ALT activity (U/L)</td>
<td>27±14</td>
<td>21</td>
<td>20±8</td>
</tr>
</tbody>
</table>

Antiviral therapy for pregnant CHB patients

- **Birth plan of women CHB in childbearing age:**
  Antiviral therapy should be completed before pregnancy: six months before pregnancy.

- **Antiviral treatment for unexpected pregnant patients:**
  Unexpected pregnancies during IFN antiviral therapy should be terminated.
  
  LAM / LdT / TDF: After fully communications, to continue.
  ADV, ETV: switch to LAM / LdT / TDF.
Treatment of hepatitis attack during pregnancy

- Antiviral therapy of normal liver function before pregnancy and hepatitis attack during pregnancy:

1. Pregnant patients with mildly elevated ALT can be closely observed or given liver symptomatic treatment temporarily, anti-viral treatment should be considered after delivery.

2. For pregnancy patients with severe liver disease, LAM, LdT, TDF can be considered for antiviral therapy after consultation and informed, the program can be reconsidered after delivery.
Transmission blocking of Pregnant women infected with HBV

Current data suggests that HBV intrauterine transmission rate is less than 5%.

- HBV DNA load of pregnancy Patients is the most important.
- Among failed immune blocking patients 90% of whose mothers are HBeAg-positive.
- Effective anti-viral therapy can significantly reduce the incidence of HBV vertical transmission: the main evidence comes from LAM, LdT with TDF.
Zhang Hua, from Beijing You An Hospital, reported a large prospective clinical study of LdT for LAM used for PMTCT in 2014. Higher baseline HBV DNA load patients from 28 weeks of gestation to four weeks after delivery should choose LAM or LdT for PMTCT.
Vertical transmission LAM / LdT for blocking HBV infection

The results showed that LAM and LdT can significantly reduce the chance of HBV transmission.
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## Antiviral treatment of patients combined with HCV infection

<table>
<thead>
<tr>
<th>HBV DNA</th>
<th>HCV RNA</th>
<th>ALT</th>
<th>Recommended programs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below detection limit</td>
<td>Can be detected</td>
<td></td>
<td>Refer to anti-HCV standard treatment regimen</td>
</tr>
<tr>
<td>Can be detected</td>
<td>Can be detected</td>
<td>&lt;2×ULN</td>
<td>Refer to anti-HCV standard treatment regimen</td>
</tr>
<tr>
<td>Can be detected</td>
<td>Can be detected</td>
<td>&gt;2×ULN</td>
<td>According to Patient's condition Using IFN-α + RBV ± Nas for treatment</td>
</tr>
<tr>
<td>Can be detected</td>
<td>Below detection limit</td>
<td>&lt;2×ULN</td>
<td>Refer to carriers’ management, Do not carry out antiviral therapy temporarily, regularly monitoring</td>
</tr>
<tr>
<td>Can be detected</td>
<td>Below detection limit</td>
<td>&gt;2×ULN</td>
<td>Refer to anti-HBV treatment</td>
</tr>
<tr>
<td>Below detection limit</td>
<td>Below detection limit</td>
<td></td>
<td>Do not carry out antiviral therapy temporarily, regularly monitoring</td>
</tr>
</tbody>
</table>

- To avoid The joint of LdT and IFN.

慢性乙型肝炎特殊患者抗病毒治疗专家共识, 《中国肝脏病杂志》2015,7(1):95-102
Antiviral treatment of patients combined with HIV infection

- HIV co-infection can increase HBV DNA level, reduce spontaneity HBeAg seroconversion, aggravation liver disease, increase liver-related mortality.

- Anti-HBV therapy should combine of the condition of HAART
  - If patients need anti-HBV and HIV treatment at the same time, anti-HBV drugs can be taken into account in HAART regimen: TDF, LAM, emtricitabine.
  - If HAART treatment is not needed temporarily, its anti-HBV treatment can select ADV, LdT and IFN-α.
  - Because monotherapy of LAM, TDF, ETV induced risk of HIV drug resistance, LAM, TDF, ETV treatment is not recommended for such patients.
ETV therapy can inhibit the HIV virus in patients combined with HIV infection

Mcmahon MA. NEJM. 2007
Antiviral therapy in patients combined with renal disease

- Antiviral treatment issues of chronic renal failure patients
  - To adjust the dosing interval and (or) dose according to creatinine clearance, whether hemodialysis, peritoneal dialysis, etc.
  - Strengthen the monitor of renal function, blood, etc.
- Antiviral therapy of HBV associated glomerulonephritis
Antiviral therapy of HBV associated glomerulonephritis

- Treatment indications
  - HBV-AG diagnosed patients
  - HBV DNA detected patients

- Treatment drugs
  - LAM: most evidence, but mostly case reports
  - ADV: Note renal function
  - LdT and ETV: No evidence
  - IFN: no consensus.

- Treatment course
  - Not exact.
Antiviral therapy of patients combined with autoimmune thyroid disease

- IFN-\(\alpha\) should not be used as antiviral therapy in uncontrolled thyroid dysfunction patients.

- Thyroid function should be closely monitored for patients with previous thyroid dysfunction or high titers of thyroid autoantibodies pre-treatment when using IFN-\(\alpha\) as anti-viral treatment.

- Antiviral therapy of IFN-\(\alpha\) in patients with thyroid dysfunction should be stopped when necessary.
Patients receiving immunosuppressive or chemotherapy

- 20% to 50% may have increased HBV DNA load, some may have transaminase elevations and elevated serum bilirubin levels, etc.

- For HBsAg carriers: NAs should be used for preventive treatment 2 to 4 weeks before immunosuppression or chemotherapy treatment.

- HBV DNA <5 log10 copies / ml: Discontinue 6 months after chemotherapy.

- HBV DNA > 5 log10 copies / ml: Continue treatment until the stopping Standard of antiviral therapy of general patients is reached.

- Virological markers of HBV and HBV DNA load should be closely monitored in HBsAg negative, anti-HBc positive patients.

慢性乙型肝炎特殊患者抗病毒治疗专家共识，《中国肝脏病杂志》2015,7(1):95-102
Summary

1. Combined with HCV / HIV infection:
   - HCV: Combine HCV RNA, ALT;
   - HIV: Combine HAART therapy

2. Combine renal disease:
   - CRF patients: Adjust dose.
   - HBV-AG: NAs, LAM

3. Combine thyroid disease:
   - Contraindications, monitoring thyroid function and autoantibody

4. Receiving immunosuppressive and Cytotoxic therapy:
   - Use NAs in advance
   - Stopping Standard
   - Anti--HBc positive patients be monitored

慢性乙型肝炎特殊患者抗病毒治疗专家共识，《中国肝脏病杂志》2015,7(1):95-102
Thank you!