慢性 B 型肝炎治療指引

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建議一:

在考慮藥物治療前，應有完整的評估及建議(II)

建議二:

除了肝臟已有嚴重纖維化(Ishak fibrosis ≧4 或 Metavir score ≧3) 且合併病毒血症的患者外，病人之 ALT 值持續正常或輕微的上升，不建議治療，但需每 3-6 月施行一次肝癌篩檢(Ⅰ)

建議三:

血清HBV DNA陽性(HBeAg陽性:每毫升大於 2×10^4IU; HBeAg陰性:每毫升大於 2×10^3IU)及ALT值大於正常值上限的二倍，應考慮治療(Ⅰ)。假如即將或已經發生肝臟代償不全時，愈快治療愈好(Ⅱ)。此外則建議觀察 3 至 6 個月(Ⅱ)。

建議四:

建議使用傳統型干擾素或長效型干擾素(Ⅰ)，干安能(Ⅰ)、干適能(Ⅰ)、貝樂克(Ⅰ) 、喜必福(I)或惠立妥(I)來治療病人，治療應考慮療效及抗藥性，如果有肝臟代償不全的疑慮時，建議使用干安能(Ⅱ)、貝樂克 1mg (I)、喜必福(I)或惠立妥(I)來治療。

建議五:

在治療中，建議至少每 3 個月需監測 ALT、HBeAg 及/或 HBV DNA(Ⅰ)，若是使用干適能或惠立妥治療，則需監測腎功能(Ⅰ)，若是使用喜必福治療，則需監測 CPK 值(Ⅰ)。在使用干擾素治療時，主要則需監測副作用的產生及建議監測 HBsAg 濃度(Ⅰ)。

建議六:

在治療結束後一年內，建議每 1~2 個月需監測 ALT ，必要時加測 B 型肝炎病毒相關標記(含 HBV DNA)，以期早期偵測出病毒的復發(Ⅱ)。對於治療失敗者，仍需進一步的監測，可以偵測出延遲性反應，在適當的時機可以考慮給予再治療的計劃(Ⅱ) 。

建議七:

使用長效型干擾素治療，建議治療 12 個月(Ⅰ)。

建議八:

使用干能安、干適能、貝樂克、喜必福或惠立妥治療，建議至少治療一年(Ⅰ)，對 HBeAg 陽性的病患，在治療至 HBeAg 血清轉換及偵測不到 HBV DNA(聚合酶連鎖反應)後，應給於鞏固療法一年再考慮停藥(Ⅱ)。對 HBeAg 陰性的病患，治療至 ALT 正常及血清 HBV DNA(聚合酶連鎖反應)偵測不到，至少有三次，每次間隔 6 個月，則可考慮停藥(Ⅱ)。若考慮 B 型肝炎病毒的抗藥性問題，則優先建議惠立妥或貝樂克治療(Ⅰ)。

建議九:

在產生干安能、喜必福或貝樂克抗藥的病患，應加上干適能的治療(Ⅱ)。在肝臟代償良好的病患，也可直接轉為貝樂克 1mg 或惠立妥治療(Ⅱ)；在肝臟代償不全的病患，直接服用干適能與干安能或喜必福合併治療，可防止因干安能或喜必福停藥後野生種的病毒迅速返回時，對肝臟代償不全的病患，會有潛在的危險。

APASL guideline 2012

Recommendation 1. Thorough evaluation and counselling are mandatory before considering drug therapy (IIA).

Recommendation 2. Patients with viral replication but persistently normal or minimally elevated ALT levels should not be treated, except in patients with advanced fibrosis or cirrhosis. They need adequate follow-up and HCC surveillance every 3-6 months (IA).

Recommendation 3. Assessment of liver fibrosis is recommended in viremic patients with high normal or minimally raised ALT levels and older than 40 except patients with clinical evidence of cirrhosis(IIA).

Recommendation 4. Chronic HBV-infected patients with ALT ≥ 2 times ULN, and HBV-DNA ≥ 2.0 x10^4 IU/mL if HBeAg positive and ≥ 2.0x10^3 IU/mL if HBeAg-negative as well as advanced fibrosis or cirrhosis with any ALT level should be considered for treatment (IA). Treatment should be started as early as possible in case of impending or overt hepatic decompensation (IA). Otherwise, 3-6 months' observation is recommended to ensure the need of therapy (IIA). Indications are similar for retreatment!

Recommendation 5. Treatment naïve patients can be treated with conventional IFN 5-10 MU 3 times per week (IB) or Peg IFN-□2a 180 □g weekly or Peg IFN-□2b 1-1.5ug/Kg weekly (IA), ETV 0.5 mg daily (IA), TDF 300mg daily (IA), ADV 10 mg daily (IB), Ldt 600 mg daily (IB), or LAM 100 mg daily (IB). Thymosin□ 1.6 mg 2 times per week can also be used (IB). ETV or TDF is the preferred Nuc.

Recommendation 6. During therapy, ALT, HBeAg and/or HBV-DNA should be monitored at least every 3 months (IA). Renal function should be monitored if TDF or ADV is used (IA). Muscle weakness should be monitored especially if LdT is used (IIIA). During IFN-based therapy, monitoring of blood cell counts and other adverse effects are mandatory (IA).

Recommendation 7. After the end of therapy, levels of ALT and HBV DNA should be monitored monthly for the first 3 months to detect early relapse, and then every 3 months in the first year post-therapy. If uneventful, monitor every 3 months (for cirrhotic patients) to 6 months (for responders) thereafter (IIA). For non-responders, further monitoring of HBV markers is required to both recognize a delayed response or to plan retreatment when indicated (IIA).

Recommendation 8. For conventional IFN, the current recommended duration of therapy is 4-6 months for HBeAg positive patients (IA) and at least a year for HBeAg negative patients (IA). For Peg IFN, the recommended duration is 12 months (IA). For thymosin□ $_1$, the recommended duration of therapy is 6 months for both HBeAg-positive (IA) and HBeAg-negative patients (IIB).

Recommendation 9. For Nucs: In HBeAg positive patients, treatment can be stopped when HBeAg seroconversion with

undetectable HBV-DNA has been maintained for at least 12 months (IIA). In HBeAg negative patients, it is not clear how long this treatment should be continued if HBsAg remains positive, but treatment discontinuation can be considered if patients have been treated for at least 2 years with undetectable HBV DNA documented on three separate occasions 6 months apart. (IIA). In compliant patients with primary treatment failure at month 3 or suboptimal viral response at month 6, switch to a more potent or add on a drug without cross resistance if LAM, Ldt or ADV was used (IIIA).

Recommendation 10-1. For female patients of child-bearing age, IFN-based therapy is preferred for nonpregnant women. Pregnancy is discouraged during IFN therapy (IA). Pregnant women who need treatment can be treated with category B Nuc(s) (IIA).

Recommendation 10-2. For the prevention of mother-to-child transmission, pregnant women with high HBV DNA (>2x10^6 IU/mL) can be treated with Ldt in the third trimester (IIA). TDF is an alternative (IIIA).

Recommendation 11. ART containing TDF + FTC/LAM is the treatment of choice for the majority of HIV-HBV coinfected individuals. If the CD4 count is greater than 500 and ART is not warranted, ADV or PEG-IFN can be considered. (IIA).

Recommendation 12. In patients with concurrent HCV (IA) or HDV infection, determine which virus is dominant and treat the patients accordingly (IA)

Recommendation 13. ETV or TDF is the agent of choice for patients with obvious or impending hepatic decompensation (IA). Ldt, LAM or ADV can also be used in Nuc-naïve patients (IB). Renal function and lactic acidosis should be monitored in this group of patients, especially those with MELD score greater than 20. (IIIA)

Recommendation 14. For patients who developed drug resistance while on LAM, add-on ADV therapy (IA) or switching to TDF is indicated (IIA); switching to ETV (1mg/day) is an option (IB) but not preferred. For patients who developed drug resistance while on ADV, add-on LAM, Ldt, ETV or switching to TDF is indicated (IIIA). For patients who develop drug resistance while on Ldt, add-on ADV therapy or switching to TDF is indicated (IIIA). For patients who develop drug

resistance while on entecavir, add-on TDF or ADV is indicated (IIIA). For patients with prior failure of or resistance to LAM or Ldt and ADV, switching to ETV plus TDF is indicated.(IIA)

Switching to IFN-based therapy is an option for patients with resistance to LAM (IA), or other Nucs. (IIIA)

Recommendation 15-1. Before receiving immunosuppression or chemotherapy, patients should be screened for HBsAg (IVA). If HBsAg positive, start Nucs treatment if clinically indicated.(IA) Otherwise, prophylactic therapy with LAM before the start and up to at least 6 months after the end of immunosuppression or chemotherapy is recommended (IA). ETV and TDF can also be used for prophylaxis (IIIA).

Recommendation 15-2. For patients going to receive anti-CD 20 agents, anti-HBc should be screened. If anti-HBc positive, HBV DNA should be closely monitored (IVA).

Recommendation 16-1. Nuc(s) should be commenced in all patients with HBV-associated liver failure who are listed for organ transplantation and have detectable HBV DNA (IVA).

For liver transplantation, LAM plus low dose HBIG (400-800 U, i.m. daily for 1 week, followed by 400-800 U monthly long-term) provide safe and effective prophylaxis against HBV reinfection of the allograft (IIA). Alternatively, LAM + ADV or ETV prophylaxis can be considered (IIA)

Recommendation 16-2. Late (at least 12 months post-transplant) HBIG substitution by ADV provides safe and cost-effective prophylaxis (IIA). Late conversion to LAM monotherapy may be considered in “low-risk” patients (IA).

Recommendation 16-3. HBV-naïve patient receiving a liver from anti-HBc (+) donor should receive long-term prophylaxis with either LAM or HBIG (IIIA).

Recommendation 17. Nuc should be commenced in all HCC patients with HBV DNA > 2000 IU/mL before and/or after curative therapy of HCC as their counterparts without HCC (IIIB). Preemptive Nuc therapy should be initiated in all HCC patients who are to receive transarterial chemoembolization (IIA)