Consensus

Chinese Consensus on Antiviral Treatment of Chronic Hepatitis B Patients with Nucleos(t)ide Analogues

Professional Staff Committee of Chinese Consensus on Treatment of Chronic Hepatitis B Patients with Nucleos(t)ide Analogues

Antiviral treatment is the main method for chronic hepatitis B (CHB). After antiviral treatment, some patients may obtain satisfactory therapeutic effect, but some patients still occurred primary non-response, suboptimal response, even resistance to nucleos(t)ide analogues or relapse, which are becoming the key problems confusing the clinical staffs. Thus, in January 2013, editorial department of Chinese Journal of Experimental and Clinical Infectious Diseases (Electronic Edition), Chinese Journal of Liver Diseases (Electronic Edition) and Infection International (Electronic Edition) organized an expert committee to form an expert consensus on antiviral treatment of CHB patients with nucleos(t)ide analogues. In this consensus, only primary non-response, suboptimal response and relapse were involved, and the management of resistance could be referred to the consensus on management of drug resistance to nucleos(t)ide analogues in patients with CHB.¹ The consensus publication promoted and standardized treatment of CHB patients with nucleos(t)ide analogues. Clinical evidence of treatment of CHB patients with nucleos(t)ide analogues is increasing. The formulation of this consensus is according to the principles of evidence-based medicine, but large number of clinical studies of combination therapy is still in progress. This consensus can not fully answered the problems encountered in antiviral the treatment of CHB patients with nucleos(t)ide analogues. With the progress of clinical practice, the evidence is accumulating continuous and professional staff committees will update the consensus. The evidence gradings in the consensus are listed in Table 1.

TREATMENT OF PRIMARY NON-RESPONSE PATIENTS WITH CHRONIC HEPATITIS B

Definition of primary non-response

Two descriptions for non-response to nucleos(t)ide analogues are defined: primary treatment failure and primary non-response. Furthermore, different guidelines showed obviously different definitions for this term (Table 2), leading to a puzzle in clinical practice. Actually, both “primary treatment failure” and “primary non-response” describe the same condition. So we suggest a standard and unified term to definite these conditions. Experts committee recommended that non-response is defined as less than 1 log₁₀ IU/ml decrease in HBV DNA level from baseline at week 12 of therapy in naïve and compliant patients who fulfilled the indications for antiviral therapy.

Evaluation of CHB patients with primary non-response

Primary non-response need to be assessed in clinical practice as follows:

Patients

Most importantly, indications for antiviral treatment should be strictly followed. Moreover, all patients should be checked for compliance including dose, administration route, strict frequency and enough treatment duration or so. All patients should be informed of possible risks after random treatment cessation in order to obtain an improved treatment compliance.

Drugs

Many studies showed that high virus load is usually associated with lower rates of virological response (undetectable HBV DNA) under monotherapy of adefovir dipivoxil (ADV), lamivudine (LAM) or telbivudine (LdT).⁶ Furthermore, adefovir dipivoxil can engender higher rates of primary non-response (10%

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Table 1. Levels of evidence criteria

Levels of evidence	Criteria
I	At least one well-designed randomized, controlled trial
II	Well-designed cohort or case-controlled trial
III	Serial case or single case report or defective-designed clinical trials
IV	Opinions of authoritative experts based on clinical experience, descriptive study or meeting reports

Table 2. Definitions of primary non-response for antiviral therapy in patients with chronic hepatitis B

Guidelines	Definitions
AASLD (2009) ²	Primary non-response: less than 2 log ₁₀ IU/ml decrease in HBV DNA level from baseline at 24 weeks of oral nucleoside/nucleotide analogues therapy, for oral nucleos(t)ide analogues therapy only
CMA (2010) ³	Primary treatment failure: less than 2 log ₁₀ IU/ml decrease in HBV DNA level from baseline at 6 months of nucleos(t)ide analogues therapy
APASL (2012) ⁴	Primary treatment failure: less than 1 log ₁₀ IU/ml decrease in HBV DNA level from baseline at 12 weeks of antiviral therapy with oral drugs
EASL (2012) ⁵	Primary non-response: less than 1 log ₁₀ IU/ml decrease in HBV DNA level from baseline at 12 weeks of antiviral therapy, for both nucleos(t)ide analogues and IFN α therapy

Notes: AASLD, American Association For the Study of Liver Diseases; CMA, Chinese Medical Association; APASL, Asia Pacific Association for the Study of Liver Research; EASL, European Association for the Study of the Liver.

- 20%) than entecavir (ETV) and tenofovir dipivoxil (TDF).

Viruses

Primary non-response may be associated with the dynamic change of HBV quasispecies and the drug-resistant mutations of HBV.⁷ Most researchers consider that if the heterology of viral quasispecies is obvious, the strains composing of viral quasispecies will be so complicated that HBV will adapt to the environment better, leading to more difficulty in antiviral therapy.⁸⁻¹²

Antiviral therapy of primary non-response patients

The correct choice of a first-line potent therapy to achieve sustained long-term suppression of viral replication provides the best chance of preventing treatment failure. With the advent of more potent antiviral drugs, such as TDF and ETV, this phenomenon, often seen with ADV, is now less frequent. When a primary nonresponse is identified, antiviral treatment should be modified to prevent disease progression and subsequent risk of emergence of drug-resistant mutants. According to the roadmap of CHB treatment,¹³⁻¹⁵ the week-12 time point on therapy is important to determine the antiviral activity of the treatment regimen and assess treatment adherence.¹⁶⁻¹⁸

Patients with suboptimal response to LAM/LdT

Previous studies showed ADV add-on therapy for these patients may improve virological response and decrease drug resistance risk.^{19,20} Other study showed TDF add-on therapy may improve virological response in primary non-response patients. Based on previous studies, it is recommended that patients with primary non-response to LAM/LdT should take ADV/TDF add-

on therapy. Switch to TDF can also be considered. But switch to ETV is not recommended, due to its cross-resistance site with LAM/LdT.²¹

Patients with primary non-response to ADV

Studies showed add-on therapy of LAM/LdT for ADV primary non-response patients may improve virological response.¹⁸ It is reported that ADV primary non-response patients took ETV switch-to therapy may also improve virological response.²² Based on previous studies, it is recommended that patients with primary non-response to ADV should take ETV, LdT or LAM add-on therapy. Switching to TDF or ETV can also be considered.

Patients with primary non-response to ETV/TDF

A small clinical trial showed TDF switch-to therapy for these patients with primary non-response to ETV may improve virological response.²³ A study in South Korea suggested that add-on ADV for ETV primary non-response patients may improve virological response.¹⁸ Study showed that for HBeAg positive patients with baseline HBV DNA ≥ 8 log₁₀ IU/ml, who took ETV and TDF combination therapy had higher virological response rate than those who took ETV mono-therapy.²⁴ Based on previous studies, it is recommended that patients with baseline HBV DNA ≥ 8 log₁₀ IU/ml should take add-on therapy of agents without cross resistance. The rate of primary non-response to TDF is low and relevant data is limited. Add-on therapy of ETV, LdT, LAM still need further study.

Patients with primary non-response to NUCs may also consider (Peg-) IFN add-on or switch-

to therapy. After 12 weeks treatment, HBV DNA, HBeAg and HBsAg levels should be detected, and the treatment strategy should be adjusted according to the results. Individualized therapy is recommended in these patients and side-effects should be monitored closely. Combination of LdT and IFN α should be avoided.

Recommendations

Primary non-response is defined as less than 1 log₁₀ IU/ml decrease in HBV DNA level from baseline at 12 weeks of therapy in naïve and compliant patients who fulfil the indications for antiviral therapy. When a primary nonresponse is identified, antiviral treatment should be modified to prevent disease progression and subsequent risk of emergence of populations of drug-resistant mutants.

Patients with primary non-response to LAM/LdT should take ADV (II)/TDF (II) add-on therapy. Switch to TDF (II) can also be considered. But switch to ETV is not recommended due to its cross-resistance site with LAM/LdT (II).

Patients with primary non-response to ADV should take ETV (III), LdT (II) or LAM (II) add-on therapy. Switch to TDF (II) or ETV (II) can also be considered.

Patients with primary non-response to ETV could switch to TDF (II) or add-on ADV (III). Patients with baseline HBV DNA ≥ 8 log₁₀ IU/ml and primary non-response to ETV should take add-on therapy of agents without cross resistance (III).

Patients with primary non-response to NUCs may also consider (Peg) IFN add-on or switch-to therapy (II). After 12 weeks treatment, HBV DNA, HBeAg and HBsAg levels should be detected, and the treatment strategy should be adjusted according to the results. Combination of LdT and IFN α should be avoided.

TREATMENT OF SUBOPTIMAL RESPONSE CHRONIC HEPATITIS B

Definition of suboptimal responses

Description of suboptimal response to NUCs in previous guidelines are shown in Table 3. In this consensus, experts committee recommended the definition of suboptimal response as a decrease in HBV DNA of more than 2 log₁₀ IU/ml, but HBV DNA detectable with sensitive real-time PCR assay after at least 24 weeks of NUCs therapy in compliant patients.

Evaluation of CHB patients with HBV DNA detectable after 24 weeks of NUCs therapy

Patients with HBV DNA detectable after 24 weeks of NUCs therapy should be evaluated thoroughly as below:

a. Initial indication of antiviral therapy: for some patients who started antiviral therapy in immune tolerance phase, antiviral therapy should be ceased with close monitoring.

b. Previous antiviral therapy: for patients who had been treated with NUCs, further antiviral treatment should be individualized according to patients' previous treatment agents, duration and virological response.

c. Compliance to antiviral therapy: for all patients with HBV DNA detectable after 24 weeks of NUCs therapy, compliance should be evaluated closely. Close monitoring is required in patients with poor compliance. HBV resistance detection should be considered in some patients since irregular drug application may promote HBV resistance to NUCs.

d. HBV resistance to NUCs: For patients with HBV DNA detectable after 24 weeks of NUCs treatment, especially in patients with virological breakthrough, HBV NUCs resistance should be evaluated. For patients with clear genetic resistance to certain NUCs, antiviral therapy should be adjusted (HBV resistance management consensus).¹

Initial indication, previous antiviral therapy, compliance and drug resistance should be evaluated closely before patients were defined as suboptimal virological response.

Antiviral therapy of suboptimal response patients

Patients with suboptimal response to LAM/LdT

Patients with suboptimal response to LAM/LdT after 24 weeks therapy have higher risk to develop drug resistance. Previous several perspective, randomized and controlled studies showed ADV add-on therapy for these patients may improve virological response and decrease drug resistance risk.^{19,26} One European multi-centered cohort study showed TDF add-on therapy may improve virological response in LdT suboptimal response patients.²⁷ Based on previous studies, it is recommended that patients with suboptimal response to LAM/LdT should take ADV/TDF add-on therapy. Switch to TDF, ETV + ADV or ETV + TDF can also be considered.

Patients with suboptimal response to ADV

ADV is a less potent agent for HBV and long-term use of ADV may also induce drug resistance in some patients. Patients with suboptimal response to ADV

after 24 weeks therapy should consider regimen adjustment. Chen et al reported a perspective and controlled study to evaluate 12 months add-on therapy of LAM/LdT for ADV suboptimal response patients.²⁸ Results showed that LAM and LdT add-on therapy may both improve virological response for these patients. But LdT add-on group had a higher rate of HBeAg seroconversion than LAM add-on group. Levvero et al reported that patients who occurred ADV suboptimal response and swithed to TDF may also improve virological response²⁹. Based on previous studies, it is recommended that patients with suboptimal response to ADV should take ETV, LdT or LAM add-on therapy. Switch to TDF or ETV can also be considered.

Patients with suboptimal response to ETV/TDF

ETV and TDF are potent agents for HBV and have high genetic barrier. Global registration studies showed that most patients who took ETV/TDF and did not achieve HBV DNA undetectable at week 24, can get complete virological response if they continued single agent therapy.^{30,31} Lok et al showed for HBeAg positive patients with baseline HBV DNA $\geq 8 \log_{10}$ IU/ml, those who took ETV and TDF combination therapy had higher virological response rate than those who took ETV mono-therapy.²⁴ Based on previous studies, it is recommended that patients with baseline HBV DNA $\geq 8 \log_{10}$ IU/ml and suboptimal response to ETV/TDF at week 24 should take add-on therapy of agents without cross-resistance. Patients with baseline HBV DNA $< 8 \log_{10}$ IU/ml and suboptimal response to ETV/TDF at week 24 should continue single agent treatment and evaluate virological response at week 48.

IFN treatment for patients with suboptimal response to NUCs

Patients with suboptimal therapy to NUCs may also consider (Peg-) IFN α add-on or switch-to treatment. Individualized therapy is recommended in these patients and side-effects should be monitored closely. Combination of LdT and IFN α should be avoided.

Recommendation

Suboptimal virological response is defined as a decrease in HBV DNA of more than $2 \log_{10}$ IU/ml, but HBV DNA detectable with sensitive real-time PCR assay after treatment for at least 24 weeks in compliant patients.

Initial indication, previous antiviral therapy, compliance and drug resistance should be evaluated in patients with HBV DNA detectable after 24 weeks of NUCs therapy.

Patients with suboptimal response to LAM/LdT should take ADV (I)/TDF (II) add-on therapy. Switch to TDF (III), ETV + ADV (IV) or ETV + TDF (IV) can also be considered.

Patients with suboptimal response to ADV should take ETV (III), LdT (II) or LAM (II) add-on therapy. Switch to TDF (II) or ETV (IV) can also be considered.

Patients with baseline HBV DNA $\geq 8 \log_{10}$ IU/ml and suboptimal response to ETV/TDF at week 24 should take add-on therapy of agents without cross-resistance (III). Patients with baseline HBV DNA $< 8 \log_{10}$ IU/ml and suboptimal response to ETV/TDF at week 24 should continue single agent treatment and evaluate virological response at week 48 (I).

Patients with suboptimal therapy to NUCs may also consider (Peg-) IFN add-on or switch-to therapy (IV) . Individualized therapy is recommended in these patients and side-effects should be monitored closely. Combination of LdT and IFN should be avoided.

TREATMENT OF RELAPSING CHRONIC HEPATITIS B PATIENTS AFTER ANTIVIRAL TREATMENT

Definition of chronic hepatitis B relapse

Definitions of chronic hepatitis B relapse are listed in Table 4.

The definition in this paper is based on a

Table 3. Suboptimal response to NUCs defined in guidelines

Guideline/Consensus	Definitions
Keeffe Roadmap Report (2007) ⁴	Partial virological response: a decrease in HBV DNA to less than $2 \log_{10}$ IU/ml but detectable after 24 weeks of therapy.
Chinese Expert Recommendation on NUCs Combination Therapy for CHB (2011) ²⁵	Suboptimal response: a decrease in HBV DNA to more than $2 \log_{10}$ copies/ml but detectable after certain duration NUCs therapy (24 weeks of LAM, LdT and ETV; 48 weeks of ETV, LLD of HBV DNA defined as $1 \log_{10}$ copies/ml).
APASL CHB guideline (2012) ⁴	Suboptimal virological response: serum HBV DNA still detectable at 24 weeks of a oral antiviral therapy in adherent patient
EASL CHB guideline (2012) ⁵	Partial virological response: a decrease in HBV DNA of more than $1 \log_{10}$ IU/ml but detectable HBV DNA after at least 6 months of therapy in compliant patients

Notes: APASL, Asia Pacific Association for the Study of Liver Research; EASL, European Association for the Study of the Liver.

Table 4. Definitions of chronic hepatitis B relapse in guidelines

Guidelines	Definitions
AASLD (2009) ²	The results of twice detections of HBV DNA with an interval of at least 4 weeks shall be $> 1 \log_{10}$ IU/ml higher than the lowest endpoint of treatment.
CMA (2010) ³	Virus response is observed at the end of treatment. However HBV DNA would re-raise or seroconvert with ALT and AST increase following drug-withdrawal, but the other factors elevating ALT and AST should be excluded.
APASL (2012) ⁴	Virological relapse: serum HBV DNA $> 2\,000$ IU/ml after drug-withdrawal in patient that obtain viral response. Clinical relapse: the serum HBV DNA $> 2\,000$ IU/ml and ALT $> 2 \times$ ULN after drug-withdrawal in patient that obtain viral response.

Notes: AASLD, American Association For the Study of Liver Diseases; CMA, Chinese Medical Association; APASL, Asia Pacific Association for the Study of Liver Research.

comprehensive consideration of guidelines and practical operability, that is, viral response could be observed at the end of treatment, but HBV DNA levels with an interval of at least 4 weeks after drug-withdrawal raise $>1 \log_{10}$ IU/ml than the lowest point of primary treatment endpoint, with or without ALT elevated, and other factors causing ALT elevation should be excluded.

Reasons and types of chronic hepatic B relapse

Due to a long half-life of HBV cccDNA replication module, it is difficult to completely clear HBV from liver by current antiviral drugs, which lead to higher relapse rate after drug-withdrawal.

Two types of chronic hepatitis B relapse are discussed here: one is for patients who received effective treatment and reached the standard of drug-withdrawal, namely patients with effective treatment and standard of drug-withdrawal. The other is for patients who received effective treatment but did not reach the standard of drug-withdrawal, namely patients with effective treatment and non-standard drug withdrawal.

The standard of drug-withdrawal for HBeAg positive patients in guideline of Chinese CHB Prevention and Treatment is: if HBV DNA undetectable, ALT normalization and HBeAg seroconversion remained followed by a consolidation therapy for at least 1 year (at least 2 reviews with an interval of 6 months), with a total course at least 2 years, then drug-withdrawal (II) could be considered, but longer duration may reduce relapse. For patients with HBeAg negative, the treatment course should be longer and drug-withdrawal (II) could be considered if patients achieving HBV DNA undetectable, ALT normalization followed by a consolidation therapy for at least 1.5 years (at least 3 reviews with an interval of 6 months and a total course treatment of at least 2.5 years. As the relapse rate is high due to drug withdrawal, a duration course should be considered.

Treatment for patients with chronic hepatitis B relapse

Relapsed patients who received effective primary treatment and reached drug-withdrawal standard

Generally, primary drugs applied for treatment are recommended. However, several studies showed that relapse could still occur in spite of strict standard of drug-withdrawal, which imply that the retreatment course should be longer.³²⁻³⁶ So low-resistance drugs such as ETV and TDF are strongly recommended in long-course treatment, concerning the resistance risk of long-term treatment.³⁷ A report showed that 192 HBeAg positive patients with LAM primary treatment could obtain HBeAg seroconversion quickly with LAM retreatment after drug-withdrawal relapse, which could not maintain for a long time. Another study showed that if patients with viral response to ETV treatment were given sequential LAM treatment, then it was hard to maintain previous response,³⁸ which showed CHB patients with relapse after drug-withdrawal should continue or switch to potent low-resistance drugs for long-term treatment (ETV or TDF).

For relapsed patients who reached standard of drug-withdrawal during NUCs primary treatment could also take NUCs combined therapy. A study showed that 53 HBeAg positive CHB patients were given LAM treatment or LAM-ADV combined treatment when they relapsed after drug-withdrawal of LAM primary treatment. ALT normalization, HBeAg seroconversion and drug-resistance were all better in the combined treatment group than single drug treatment group. So combined treatment is a better option for relapsed patients after drug-withdrawal with single treatment.³⁹ There should be no cross-resistance among the drugs applied in the combination therapy.

So far there is still no agreement on potent single treatment or NUCs combined treatment. For relapsed patients with higher viral load (HBV DNA $> 1.0 \times 10^7$ IU/ml), the combined treatment is recommended. For relapsed patients with viral load $< 1.0 \times 10^7$ IU/ml,

single treatment with potent and low-resistance NUCs could also be applied. HBV DNA should be detected at 24 weeks. An optimized combined treatment should be considered if the response is not optimal (HBV DNA level decreases $<2 \log_{10}$ IU/ml compared with the level before treatment).⁴⁰

Relapsed patients with effective treatment but without standard of drug-withdrawal

Treatment continuing is recommended and the regimen could refer the protocol of relapsed patients after effective treatment with standard of drug-withdrawal. But some evidences showed that although patients receiving LAM treatment did not occur drug-resistance, the long-term resistance become obviously higher after switching to ETV treatment. So combination with ADV is recommended as early as possible for these cases.⁴⁰

Recommendation

Definition of chronic HBV relapse: viral response could be observed at the end of treatment, but HBV DNA levels with an interval of at least 4 weeks after drug-withdrawal raise $>1 \log_{10}$ IU/ml than the lowest point of primary treatment endpoint, with or without ALT elevated, and other factors causing ALT elevation should be excluded (II).

Recommendation for relapsed patients who received effective treatment and reached standard of drug-withdrawal is to continue the primary treatment. However due to the resistance risk of a long-term treatment, it is recommended to choose potent low-resistance drugs (ETV and TDF) for a long-term treatment (II).

Relapsed patients who reached standard of drug-withdrawal in primary NUCs treatment could receive NUCs combined treatment. Especially the patients with viral load $<1.0 \times 10^7$ IU/ml could be given potent low-resistance single NUCs treatment, with observation of their viral load at 24th week. If the response is poor (HBV DNA level decrease $<2 \log_{10}$ IU/ml than primary treatment), then combined treatment could be considered (II).

Relapsed patients who received effective treatment but without standard of drug-withdrawal should be given a retreatment based on the same principles of patients reaching standard of drug-withdrawal (II).

For patients who received LAM treatment without resistance, the long-term resistance become obviously higher after switching to ETV treatment. So combination with ADV is recommended as early as possible (II).

Relapsed patients who received effective NUCs

primary treatment (including those who reaching drug-withdrawal standard or not), could also switch to interferon treatment alone or combined with NUCs (LdT is excluded) (III).

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