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The current status of combination therapy of Chronic Hepatitis B

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Abstract. – In the past decade, the treatment of chronic Hepatitis B (CHB) has been revolutionized by the increased availability of effective antiviral agents. However, there is an alarming of the increasing rates of viral resistance and suboptimal response in CHB patients with single drug therapy. Recently, the strategy of combination therapy for CHB has been proposed and concerned by clinicians. In this review, using PubMed and web of science as main searching tools, we evaluated various latest research reports on combination therapy for CHB, and made a summary of the progress of combination antiviral therapy and outline areas that need to be addressed in the future.

Key Words:
Chronic hepatitis B, Combination therapy, Advantage, Candidates, Strategy.

Introduction

Hepatitis B virus (HBV) infection is a serious global public health problem, and approximately two billion people who have been infected worldwide. Of them, there are more than 350 million who are chronic carriers of HBV[1, 2]. Sufficient evidences have showed that the level of serum HBV DNA is a strong predictor of HBV-related complications[3]. And how to effectively control and even eliminate virus replication has been concerned increasingly by clinicians[4,5].

At present, several drugs with different modes of action are approved and recommended as monotherapies for treatment of chronic HBV (CHB) infection[6-8]. Though those therapies rarely eradicate HBV infection, they can maximally suppress viral replication and reduce the risk of disease progression and complications.

Recently, it has been reported that the antiviral efficacy of current treatment would be affected by the interaction of multiple factors, such as specific host factors, complexity of viral quasispecies, and types of agents[9-12]. With the extension of duration of treatment, issues of drug resistance, viral relapse and particularly suboptimal response to current antiviral agents are increasingly evident[13-17], and how to manage those patients after initial therapy failure has become the primary concern for clinicians[5]. Fortunately, combination therapy as a new therapeutic direction has gained more and more attention in rescuing of initial inefficacious therapies and optimizing suboptimal response of current unsatisfactory monotherapies[18-21]. In the treatment of subset patients, evidences suggested that combination therapy could offer more advantages including synergistic anti-viral effects and a higher barrier towards resistance[22-25]. In this article, we will make a summary of the progress of combination antiviral therapy and outline areas that need to be addressed in the future according to the latest research reports.

Limitations of Current Monotherapy

With the available of highly potent nucleos(t)ide analogues (NAs)[26], entecavir (ETV) or tenofovir (TDF) monotherapy has been favored by various international guidelines[18-20]. If one starts treatment with those highly potent agents, discussions about combination therapy would be superfluous because of the low rates of resistance and failure of treatment[27, 28].

Though ETV and TDF have been developed, lamivudine (LAM), adefovir (ADV) and telbivudine (LdT) remain the mainstay therapy in many countries with high HBV prevalence (for example, in China) because of a lower cost[21]. Evidences have showed that those agents have significant drawbacks. Because of low genetic barrier to resistance, monotherapy with these agents would easily result to the emergence of drug-resistant viral strains[29]; and for inefficient inhibition of virus

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replication, suboptimal response is also common in naive patients with high viremia[17,30]. According to the current published literatures, LAM-associated resistance developed in 70% patients after 5 years of therapy, ADV-associated resistance developed in 29% patients after 5 years of therapy, and LdT-associated resistance developed in 32% patients after 3 years of therapy. The emergence of these drug-resistant strains would limit therapeutic options for individual patient. Evidences have showed that detectable serum HBV DNA level was still found in 68% of HBeAg-positive patients and 29% of HBeAg-negative patients receiving LAM treatment, and in 55% of HBeAg-positive patients and 20% of HBeAg-negative patients receiving LdT treatment[31,32]. Many studies also have suggested that the prognosis of patients with long-term suboptimal response is disappointing and those patients would be more easily to develop resistance, which would inevitably not only diminish the beneficial effects of previous therapy but also limit their future therapeutic options. Besides NAs, interferon alfa (IFN-α), an immunomodulator also have been widely used for monotherapy options. However, its antiviral efficacy is not satisfactory, and many studies suggested that IFN-α is not so potent in suppressing HBV DNA[33]. Additionally, patients with genotypes C and D responded less frequently as compared to patients with genotype A and B[34].

Thus, when and how to treat those who were with failure or poor responses to NAs or IFN-α monotherapy have become the focus of our clinical researches.

The Significance of Combination Therapy

In view of the shortcomings of current monotherapy, the challenge now is to define the most effective use of the currently available agents to enhance antiviral efficacy while avoiding the emergence of viral resistance.

The concept of combination therapy is well established for patients with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections[35,36], but combination therapy is not restricted to HIV and HCV infections. Recently, some reliable clinical studies suggested that combination therapy for HBV would also bring synergistic antiviral effects and a higher barrier towards resistance compared with monotherapy[16,37]. Experimental data showed that the combination therapy could not only inhibit viral synergy in duck hepatitis B virus (DHBV)-infected primary hepatocyte cultures, but also decrease the pool of cccDNA in already chronically infected cells in a more effective way than monotherapy[37,38].

One major benefit of combination therapies for chronic hepatitis B (CHB) is that they could significantly delay or decrease the emergency of drug resistance[39,40]. Compared to sequential NAs monotherapy, multi-drug resistance was less frequently in combination therapy[41-43]. Recently, some investigators dynamic observed the genetic evolution of viral quasispecies in patients who received, sequentially, monotherapy and combination therapy, and their findings indicated that the combination therapy could be more effective in inhibiting viral replication and reducing the complexity of HBV quasispecies[41,44].

Combination therapy as a new therapeutic direction has gained more and more attention in management of patients who responded poorly to single drug treatment[5,16], because a lot of evidences have indicated patients with poor response during treatment are more likely to develop resistance[45]. Clinical studies have shown that combination therapy can help patients who respond poorly obtain more rapid achievement of undetectable HBV DNA. Recently, one study has compared effect of ADV add-on LAM versus switching to ETV in LAM-resistant CHB patients, and they found that combination therapy was more effective in inducing complete viral suppression[46,47].

Additionally, despite combination therapy may seem costlier than monotherapy in the short term, when used appropriately, combination therapy causes significant savings: slower development of resistance, lower treatment failure rate and consequently, lower risk of end-stage liver disease.

Candidates for Combination Therapy

According to present recommendations of guidelines and clinical experience, combination therapy is only recommended for a limited number of patients with CHB, which include: patients with evidence of drug resistance so as to minimize the risk of multidrug-resistant HBV with sequential monotherapy; patients with suboptimal response to current single antiviral agent (NAs or IFN-α); patients who can least afford to develop drug resistance from a clinical perspective, for example, patients with decompensated cirrhosis and/or with HBV recurrence after liver transplantation[48]; patients with HIV/HBV coinfection on antiretroviral therapy[49,50]; patients with the high risk of resistance development during

therapy with NAs, for example, patients with long-standing HBV infection and high viraemia levels at baseline associated with more complex viral quasispecies[51,52]. More and more evidences suggest, if viral replication in those patient is well controlled, the risk of rapid disease progression and life-threatening complications could be significantly reduced[53,54].

Current Combination Therapy Strategies

Combination therapy represents the future of treatment for CHB, and ideal combination therapy should target distinct steps of the HBV life cycle, probably consisting of different classes of agents. To date, combinations of two NAs and of IFN-α and NAs are investigated widely, and they have been regarded as the main combination strategies at present. Considering NAs and IFN-alpha□having different mechanisms of antiviral action[55], the combining IFN-a with NAs seems to be the most appealing approach at present. Nevertheless, any kinds of combination have its own certain advantages and disadvantages.

De Novo Combination Therapy

Studies on the efficacy of *de novo* combination therapy with NAs are scarce and combinations of NAs are not routinely recommended as first-line treatment for ordinary patients. But for patients with long-standing infection, high viremia levels and pre-existing viral resistance strains to NAs are the most likely to benefit from *de novo* combination therapy. For patients with decompensated cirrhosis and/or with HBV recurrence after liver transplantation, *de novo* combination therapy of NAs also should be considered, because the recurrent viremia would lead to clinical deterioration.

At present, there are no data to support *de novo* combination therapy with NAs that have a high barrier to resistance in NAs-naïve patients, but combination of less potent agents may be preferable. Recently, someone evaluating the *de novo* combination of LAM and ADV versus ETV monotherapy for HBeAg-negative patients showed that LAM plus ADV combination and ETV monotherapy had similar efficacy in HBV DNA reduction and ALT normalization during the 48-week treatment period[56]. Additionally, NAs-naïve patients with HBeAg-positive disease receiving LAM plus ADV combination therapy for 2 years had less virological breakthrough compared to those receiving LAM monotherapy (19% vs 44%)[57].

Currently, the data of combination therapy of INF-α and NAs are mainly on naïve CHB patients. pegIFN-α-2b in combination with LAM showed a greater decline in HBV DNA compared with pegIFN-α-2b alone (approximately 5 log10 vs 2 log10 decline), as well as a higher rate of HBeAg loss (44% vs 29%) by the end of 52 weeks of treatment[23,58]. In Phase III trials of pegIFN-α-2a, combination of LAM and pegIFN-α-2a induced a greater decline in HBV DNA than pegIFN-α-2a alone, or LAM monotherapy at the end of treatment (HBeAg positive, 7.2, 4.5, and 5.8 log decline, and HBeAg-negative, 5.0, 4.1, and 4.2 log decline, respectively)[24,59]. These studies also found lower rates of resistance to LAM when it was administered in combination with pegIFN-α, presumably as IFNalso effective against HBV resistant mutants. Compared to those with LAM monotherapy, the rates of HBsAg clearance and seroconversion in patients with combination therapy were markedly higher[60]. The *de novo* combination therapy of ADV plus interferon-alpha also has been investigated. Evidences from a multicentre randomized controlled trial for compensated HBeAg-negative CHB showed that HBV DNA undetectable rate was higher in pegIFN-α-2a and ADV combination therapy as compared to pegIFN-α-2a monotherapy (67% vs 37%, $p = 0.02$)[61]. Another small study suggested pegIFN-α-2b in combination with ADV could lead to strong HBsAg reduction and intrahepatic cccDNA decline[37]. Because of peripheral neuropathy, the combination of IFNplus LdT was forbidden in clinical[62]. Further trials of pegIFN in combination with TDF or ETV, are required. And the combination of pegIFN and NAs may be the most promising *de novo* combination therapy strategies.

Combination Therapy for Drug-Resistance

Increasing data show combination therapy is a highly effective tool for drug-resistance patients, and it is established that combination therapy achieves better long-term efficacy and lower multidrug resistance compared with sequential monotherapy, once viral drug resistance has developed.

Several clinical trials have demonstrated the added value of combination therapy in terms of viral load decline, prevention of drug resistance and durable prevention of virologic and clinical breakthrough[46,63-69]. A 3-year study of 145 LAM-resistant patients under prolonged combination therapy of ADV and LAM showed that 80% of

LAM-resistant patients cleared serum HBV DNA and 100% remained free of virologic and clinical breakthroughs; and the 1-, 2-, 3-, and 4-year cumulative rates of *de novo* rtA181T (antiviral drug selected hepatitis B virus) were only 1%, 2%, 4%, and 4%, respectively[67]. Additionally, as compared to switch-to ETV monotherapy, ADV add-on treatment suppresses HBV replication more effectively, and decrease genotypic resistance more significantly[40,46]. However, ADV add-on therapy may have limitations in patients with a higher baseline HBV DNA in LAM rescue therapy[47]. If TDF is available, the add-on of TDF may be more potent than ADV for LAM-resistant patients[70].

In clinical practice, the add-on of LAM, LdT or ETV has been widely used for rescuing ADV-resistant patients[20]. Recently, experimental evidence indicated the rtA181T mutant strains displayed a reduction in susceptibility to both LAM and ADV[71]. So for ADV-resistant patients with detection of rtA181T, add-on of LAM was not appropriate, instead add-on of LdT or ETV is worth considering. Recently, it had been reported that TDF plus LAM could safely and markedly suppress HBV replication in patients with resistance to ADV[72].

For patients with ETV resistance, the efficacy of ETV plus ADV was still controversial[5, 73]. Jeon et al[73] reported ETV plus ADV combination therapy effectively reduced serum HBV DNA levels in patients with CHB who developed resistance to both LMV and ETV; but Kim et al[5] in their observation found that either the combination of ADV plus ETV or ADV plus LAM brought limited efficacy. To clarify this issue, long-term and large-sample studies are needed urgently.

Taking into account the immunomodulatory effects of IFNs and its potential to act with the antiviral action of NAs, the combination of IFNs with NAs is attractive. Though the studies of IFN-α combined with NAs in recurring NAs-resistant patients is limited. Some experts still suggested that the combination of IFNs plus NAs was worthy of consideration not only for reducing *de novo* resistance but also as an option for the management of those patients in whom drug resistance had already developed[74].

Combination Therapy for Suboptimal Response

Suboptimal response is encountered with all NAs therapies, which would result to poor long-term efficacy and greatly increase the incidence of resistance. Currently, there is no consensus on a definition of suboptimal response but two definitions are prevalent: a decrease in HBV DNA of more than 1 log10 copies/mL but detectable HBV DNA by real-time PCR assay; HBV DNA > 4 log10 copies/ml after more than 24 weeks of antiviral therapy. According to European Association for the Study of the Liver (EASL) Clinical Practice Guidelines, suboptimal response should be assessed at 24 weeks of treatment for moderately potent drugs or drugs with a low genetic barrier to resistance (LAM and LdT) and at 48 weeks of treatment for highly potent drugs, drugs with a higher genetic barrier to resistance or drugs with a late emergence of resistance (ETV, ADV and TDF).

In case of suboptimal response to NAs, treatment adding-on a second drug without cross-resistances should be an efficient salvage strategy. In patients receiving LAM or LdT with a suboptimal response at week 24, addition of a more potent drug that does not share cross-resistance with the existing drug could be considered (add ADV or TDF to LAM or LdT). In patients receiving ADV, ETV or TDF with a suboptimal response at week 48, adding-on a second drug for combination therapy may prevent resistance in the long term[18]. A short-term observational study evaluated the combination of LAM and ADV for HBeAg-positive patients with suboptimal response to ADV monotherapy, and reported that combining LAM and ADV for 24 weeks could induce 35.5% patients with undetectable HBV DNA, 34.5% patients with HBeAg loss and 6.9% patients with HBeAg/Anti-HBe seroconversion[16]. Additionally, we also found that both add-on LAM and add-on LdT could significant decrease in HBV-DNA, but HBeAg/Anti-HBe seroconversion was higher in add-on LdT therapy (unpublished data). For patients with suboptimal response to ETV, it has been reported that the combination of ADV plus ETV may be more effective than the combination of ADV plus LAM[75]. Unfortunately, the data of NAs plus IFNs combination therapy on patients with suboptimal response to NAs or IFN is rare.

In summary, more and more evidences have demonstrated the benefit of an early add-on treatment, as soon as suboptimal response is determined. Combination therapy would become the first-choice approach in the management of CHB patients with suboptimal response.

Combination Therapy for Decompensated Cirrhosis

Suppression of viral replication has resulted in reduction of hepatic necroinflammation and improvement of liver function in patients with decompensated cirrhosis. CHB patients with decompensated cirrhosis should be considered for antiviral therapy irrespective of HBVDNA levels. Indeed, potent NAs with good resistance profiles (ETV or TDF) could be used alone, while moderately potent drugs or drugs with a low genetic barrier to resistance (LAM, ADV, and LdT) should be used in combination[76]. A study of 115 patients with decompensated cirrhosis reported that the HBV DNA undetectable rate of combination therapy of LAM plus ADV was high to 86.7% as compared to 60.0% of LAM monotherapy; and the accumulative total mortality or liver transplantation rate was also lower in combination therapy (16.7% vs 20.0%)[77]. These findings suggested that LAM plus ADV combination therapy was a better choice for patients with decompensated cirrhosis as compared to LAM monotherapy. However, a growing number of studies referred that patients with decompensated cirrhosis would benefit more from *de novo* combination therapy as compared to add-on combination therapy, in terms of Child-Pugh score, virus inhibition and renal function[78].

Additionally, other combination strategies also should be investigated so to determine the best strategy for achieving rapid and prolonged suppression of viral replication, obtain clinical stabilization and delay or prevent the need for transplantation.

Combination Therapy for HBV Recurrence After Liver Transplantation

The combination of hepatitis B immunoglobulin (HBIG) and NAs is currently recommended for prevention against HBV recurrence after liver transplantation, but the optimal protocol is controversial. The results from a recent systematic review showed that the combination of HBIG plus ADV is associated with a lower rate of HBV recurrence than HBIG plus LAM after liver transplantation, and in patients receiving HBIG plus LAM, HBIG should be given at high dosage during the first week after liver transplantation, while lower HBIG dosage can be safely used in patients receiving HBIG plus ADV[79]. At present, HBIG administration is costly and inconvenient. So the combination of nucleoside and nucleotide analogues has been concerned. A multicenter randomized study reported that that combination of ADV plus LAM provides equivalent protection against recurrent HBV infection but better tolerability and less cost, as compared to HBIG plus LAM combination[80].

Although there are few studies of ETV or TDF being used for prevention against HBV recurrence, the properties of these drugs suggest that they are definitely required and should replace LAM or ADV for treatment[81].

Combination Therapy for HBV and HIV Co-Infection

Combination emtricitabine (FTC) or LAM with TDF is the recommended first-line strategy for treatment in chronic HBV/HIV co-infection[82]. Given its potential anti-HIV activity, both ETV and LdT must only be prescribed with antiretroviral agents[83]. For example, among patients with previous TDF/FTC failure therapy, add-on ETV can be considered to suppress viral replication[84].

Conclusions

For CHB patients who are suboptimal response to single NA therapy, at high risk of complications in the event of virological breakthrough, or already with drug-resistant HBV, combination therapy should be recommended. But for the typical CHB patients requiring antiviral therapy, under the available of highly potent antiviral agents (such as entecavir and tenofovir), there is insufficient evidence to recommend combination therapy as initial treatment. It is worth to mention here that there are no uniform combination protocols at present, and how to make reasonable combination of existing antiviral drugs, and help patients obtain more benefits from combination therapy is worth studying for us in future. In future research, the combination of a limited course of interferon with long-term nucleoside analog therapy should be more concerned. Because of rare safety data at present, close attention must be paid to the safety and adverse events of long-term combination therapy in future.

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Conflict of Interest

None.

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