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Review Article

Current Trends of Combination Therapy in Chronic Hepatitis B Management in China

Abstract

In the past decade, five oral nucleos(t)ide analogs and two formulations of pegylated interferon alpha have been approved for the treatment of chronic hepatitis B (CHB). Due to low personal income and inadequate health care system, low-to-moderate genetic barrier antiviral drugs are still widely used in China, which brings increased suboptimal response, viral relapse and resistance in real-life clinical practice. Combination therapy is a relative good approach to deal with these dilemma in Chinese CHB patients, and the strategies include de novo combination, rescue combination therapy, and optimized combination therapy. At present, combination therapy could be sonsidered for those who have suboptimal response to antiviral drugs, at high risk of complications in the event of virological breakthrough/rebound, or already with drug-resistant hepatitis B virus infection.

Introduction

Despite the availability of hepatitis B immunization, hepatitis B virus (HBV) infection remains a major public health problem in China, with an estimated 7.18% rate in the general population [1]. It is well-known that persistent elevation of serum HBV DNA levels are associated with increased risk of cirrhosis and hepatocellular carcinoma (HCC) development [2,3], and complete suppression of HBV DNA replication is the most effective way to improve the outcomes of chronic hepatitis B (CHB) [4,5].

In the past decade, five oral nucleos(t)ide analogs(NAs) and two formulations of pegylated interferon alpha (PegIFNα) have been approved for CHB treatment [6], and high potent entecavir (ETV), tenofovir (TDF) as well as PegIFNα are recommended as first-choice drugs by many international guidelines [7]. Though those agents rarely eradicate HBV infection, they can maximally suppress viral replication and reduce the risk of disease progression and complications. However, due to low personal income and inadequate health care system, low-to-moderate genetic barrier antiviral drugs such as lamivudine(LAM), adefovir dipivoxil (ADV) and telbivudine(LdT) are still widely used in China, which brings an alarming of the increasing rates of suboptimal response [8-10], viral relapse and resistance in real-life clinical practice [11,12]. How to deal with these dilemma has become the primary concern for CHB treatment.

Discussion

In China, the low-to-moderate genetic barrier antiviral agents are still recommended by Chinese Society of Hepatology and Chinese Society of Infectious Diseases [13]. Currently, approximately 50% of CHB patients are being or previously treated with these agents in China, and majority of them are treated with LAM and ADV (including generic drugs). It is worth to mention that this situation is different from that in Europe and the United States and some other developed countries.

It has been reported that the drug resistance would develop in 70% of patients after 5 years with LAM therapy, 29% of patients after 5 years with ADV therapy, and 32% of patients after 3 years of LdT therapy [14]. Therefore, the present situation of antiviral therapy in China is not optimistic. Except for the relatively cheap price, we think the outdated hepatitis B guideline knowledge of the physicians, especially those in the grassroots medical institutions, also should play extremely important roles in the widespread use of these low genetic barrier antiviral agents.

Evidences have suggested that the emergence of HBV resistance would easily diminish the biochemical and virological benefits from previous antiviral therapy. And the resistance could also limit the future therapeutic options for individual patient, because of the possible cross-resistance between different NAs. Recently, suboptimal virological response has gained more and more attentions [15]. According to the published literatures, suboptimal virological response could be found in 68% of HBeAg-positive and 29% of HBeAg-negative patients with LAM, and in 55% of HBeAg-positive and 20% of HBeAg-negative patients with LdT [16,17]; and this rate would be more higher in ADV-treated patients. Because of the unsatisfactory inhibition of HBV replication, the problem of suboptimal response also common in PegIFNα-treated patients, especially in patients with genotypes C and D [18,19]. It has been revealed that the prognosis of patients with long-term suboptimal response is also disappointing, and those patients would be more easily to develop drug resistance and viral relapse, which is correlate with increased risk of HCC development.

Recently, the combination strategies for rescuing and optimizing CHB patients who experienced failure or unsatisfactory antiviral therapy has been proposed and widely concerned [20,21]. As compared to sequential NAs monotherapy, combination therapy has significant advantages in inhibiting viral replication and reducing the risk of multi-drug resistance [22-25]. At present, combination therapy has been recommended for the following cohorts in China: patients with virological breakthrough or rebound regardless of the evidence

of drug resistance; patients with suboptimal virological response or no response to prior NAs or PegIFNα treatment; patients who cann't afford to develop drug resistance from a clinical perspective (for example, patients with decompensated cirrhosis and/or with HBV recurrence after liver transplantation[26]); and patients with the high risk of resistance development during NAs treatment.

Theoretically, the ideal combination therapy should target distinct steps of the HBV life cycle, thus the combinationn of PegIFNα and NAs seems to be the most appealing approach, because they have different mechanisms of antiviral action [27]. However, due to the alternative drug is very limited, current strategies of combination therapy also includes two different NAs combination in real clinical practice. According to the difference in startup time, combination therapy could be divided into three categories, which includes de novo combination, rescue combination therapy, and optimized combination therapy.

At present, de novo combination of NAs are not routinely recommended as first-line treatment for ordinary CHB patients[14], because high potent ETV and TDF monotherapy could achieve an ideal inhibition of HBV DNA replication. However, if ETV or TDF is not available, the de novo combinationof less potent agents could be considered, as it would bring benefits to those who has high viremia levels and pre-existing viral resistance strains to NAs. In addition, this de novo combination therapy also could be considered for those who have decompensated cirrhosis and/or with HBV recurrence after liver transplantation, because the uncontrolled HBV replication may easily lead to rapid deterioration of liver functions. Recently, the de novo combination of NAs and PegIFNα is also reported, and the combination of ADV and PegIFNα has attracted the most attention. Except for a higher HBV DNA undetectable rate [28], the de novo combination of ADV and PegIFNα also could lead to a strong HBsAg reduction and intrahepatic cccDNA decline [29]. However, there seems to be no significantly improvement of the curative efficacy of PegIFNα and LAM as compared to that of PegIFNα monotherapy [30]. Sufficient evidences have suggested that rescue combination therapy should be performed in patients with virological breakthrough or rebound. Indeed, clinical and virological studies have demonstrated the benefit of an early treatment adaptation, as soon as viral load increases [31,32]. As compared to sequential monotherapy, rescue combination therapy could achieve a durable HBV DNA inhibition and rare multidrug resistance [32-40]. One famous 3-year follow up study of 145 LAM-resistant patients under prolonged ADV+LAM combination 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 were only 1%, 2%, 4%, and 4%, respectively [38]. As compared to switch-to ETV monotherapy, the combination of LAM+ADV suppresses HBV replication more effectively and results in a significantly lower genotypic resistance [33,41]. Considering that the rtA181T mutant HBV displays a reduction in susceptibility to LAM [42], add-on LAM is not appropriate for ADV-resistant patients with this mutation. Instead, add-on of LdT or ETV should be considered, if unable to get TDF.

Optimized combination therapy is an optimization strategy based on the Roadmap concept, which is supposed to improve the clinical outcomes of patients with suboptimal antiviral response [43]. Optimized combination therapy shoud be lanuched at 24 or 48 weeks after initial antiviral therapy. For patients with suboptimal response to LAM or LdT at week 24, the optimized combination therapy of ADV or TDF add-on may be considered; while for patients with suboptimal response to ADV, ETV or TDF at week 48, the optimized combination therapy of a second drug add-on without cross-resistances may be considered. It is worth to mention that different combination strategy would result in different responses. For patients with suboptimal response to ADV, though both LAM and LdT add-on combination therapies could decrease the HBV DNA level remarkably, LdT add-on treatment could induce a significantly higher HBeAg seroconversion than LAM add-on treatment [44].

With the support of the Chinese government, Chinese scholars have made great progress in optimized combination therapy. A recent study reported by Prof. Hou JL and his research team evaluated the efficacy at week 104 of LAM monotherapy, LAM plus ADV combination therapy, and LAM optimization strategy in HBeAg positive CHB patients. Their findings showed that the combination of LAM and ADV exhibited effective viral suppression and relatively low resistance; and in LAM-treated patients with suboptimal virological response at week 24, promptly adding on ADV is necessary to prevent resistance development [45]. Additionally, a multicenter open-label randomized controlled study was also performed to evaluate the efficacy of ADV add-on combination therapy in 204 HBeAg-positive suboptimal responders of LdT monotherapy, and the results suggested that ADV add-on combination therapy could induce an additive antiviral potency, with 71.1% achieving virological response at week 104 and only 0.5% developing genotypic resistance, compared with 46.6% who achieved virological response and 37.8% who developed genotypic resistance with LdT monotherapy [46].

Conclusion

Due to low personal income and inadequate health care system, low-to-moderate genetic barrier antiviral drugs are still widely used in China, which brings increased suboptimal response, viral relapse and resistance in real-life clinical practice. Combination therapy is a relative good approach to deal with these dilemma in Chinese CHB patients, and the strategies include de novo combination, rescue combination therapy, and optimized combination therapy. At present, combination therapy could be sonsidered for those who are suboptimal response to low-to-moderate genetic barrier antiviral drugs, at high risk of complications in the event of virological breakthrough/rebound, or already with drug-resistant HBV. However, there is no uniform combination protocol 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.

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