Treatment of Chronic Hepatitis B

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ABSTRACT

Chronic hepatitis B is still a major health problem in Indonesia. Unfortunately, to date, treatment of chronic HBV (Hepatitis B virus) infection had not shown satisfactory result. Monotherapy with alpha interferon or lamivudine have been widely used as treatment of chronic HBV. However, treatment response to Alpha interferon in Asian people was not satisfactory (15% - 20%), while monotherapy with lamivudine was not sufficient to eradicate HBV in chronically infected patients and commonly induce drug resistance. The occurrence of chronic hepatitis B resistant to lamivudine had encouraged development of newer agents such as adefovir, entecavir, emtricitabine and nucleoside analog. New therapeutic strategy using combination therapy should be considered if there is no sufficient response to monotherapy.

***Keywords**: Treatment, chronic hepatitis B, combination therapy*

INTRODUCTION

Hepatitis B virus (HBV) infection is one of the most frequent of viral infection affecting human beings world-wide. An estimated 350 million persons or 5% world population are chronically infected with HBV. HBV infection is a serious health problem in Pasific-Asia. Chronic prevalence of HBV in Asia is very high and approximately 25% - 40% of chronic carriers would die due to liver disease (cirrhosis with or without hepato-cellular carcinoma).[1-6] Mean while in Indonesia, about 4% from general population of people beyond 15 years old had already been infected.

The pattern of HBV infection in Asian people is different from those in western countries. In Asia, most people usually got infected because they were born from HBV infected mothers. They also rarely had acute clinical syndrome, but infected chronically and at high risk of developing cirrhosis and hepatocellular carcinoma (HCC). In western population, HBV infection is commonly seen in injecting drug user and sexual transmitted. Acute clinical syndrome is a common feature and rarely become chronic disease. These differences were assumed by the experts to influence treatment response.[3]

Current treatment of chronic HBV infection that has been widely recommended are interferon (IFN-α) and lamivudine. Treatment response to IFN- α in Asian people was not satisfactory (15 - 20%), while monotherapy with lamivudine was not sufficient to eradicate HBV in chronically infected patients.[1] Combination therapy of new class of various drugs with various mechanisms such as adefovir dipivoxil, entecavir, emtricitabine and nucleoside analog had shown better results.[1,7] In this paper will be discussed about various drugs used in new therapeutic strategies for HBV infection and their treatment response.

CHARACTERISTICS

HBV belongs to the family of hepadnavirus and its genome is a relaxed circular, partially double stranded DNA of approximately 3,200 - 3,500 base pairs. There are partially 4 partially overlapping open reading frames encoding the envelope (S-surface), core (C), polymerase, and X viral protein gen.[8]

The replication cycle of HBV begins with the attachment of the virion to the hepatocyte. The synthesis of the plus strand HBV DNA is completed and the viral genome is converted into a covalently closed circular DNA (cccDNA).[9] In the early stage of

replication, mRNA molecules which has varied length of chain is originated from negative chain of cccDNA. Among them is pre-genomic RNA which had longer chain than RNA. This pre-genomic RNA is transferred into cytoplasm and functions as mRNA for abundant viral protein including HBsAg, HBcAg and considerable amount of DNA polymerase/reverse transcriptase. Reverse transcriptase will bind with its own mRNA and direct mRNA complex polymerase into immature viral nucleocapsid inside the cytoplasm. Pre-genomic RNA is reverse transcribed into the minus strand HBV DNA in the nucleocapsid and at the same time its RNA will be degraded. Minus strand HBV DNA will form positive partially long chained strand HBV DNA. Some part of double stranded DNA will migrate into endoplasm reticulum, where it receives its capsule and become complete virion and ready to enter the blood circulation. However, some of double stranded DNA will be transported from cytoplasm into the nucleus and form more cccDNA, thus it will have more restored intranuclear cccDNA. In single hepatocyte, it is predicted to have 10-50 copies of cccDNA.[9]

In human, the virus is found in blood and any body fluid such as saliva, semen, nasopharingeal secret and menstrual fluid. Sometimes it can also be found in urine, bile salt, pancreatic secret, pleural fluid, ascitic fluid, cerebrospinal fluid, lacrimal secret, breast milk but not gastric fluid.

IMMUNOPATHOGENESIS[10]

The virus enters the susceptible body through injection or skin. In the body, it is transferred to the liver as its main site of infection via blood circulation. Virus replicates in the liver efficiently mainly involving hepatocytes. One single virion is already sufficient to cause infection. Viremia may reach > 10^9 virion/ml and disseminate to other organs such as kidney, pancreas, testis, ovary, spleen and lymphoid glands. It remains unclear whether the immunologic activation is taken place in the liver or other site during primary infection. Whatever the exact mechanism is, immune response is strongly directed to the infected liver.

Hepatocelullar damage is predicted begin with recognizing by T cell cytotoxic through specific antigen (CTLs) which induces positive hepatocyte apoptosis. Cytotoxic T lymphocyte (CTL) will then mobilize non-specific inflammatory cells (macrophage, neutrophill and other lymphocytes) and make focal necroinflammation. Infiltration of inflammatory cells has role in hepatocelullar death. At this phase, clinical symptoms of hepatitis become apparent and together with elevation of aminotransferase enzyme. During limited acute infection, pathologic appearance is mild to moderate and viral replication is effectively controlled by host immune response and hepatitis will resolve.

In some conditions, nonspecific viral response will be enhanced by unclear host determinants or by viral factor which causes massive hepatocellular damage and fulminant hepatitis. On the other hand, chronic hepatitis occurs due to persistent liver damage caused by ineffective viral clearance. In carriers without symptoms, tolerance to HBV Ag is mild or does not cause damage in infected liver. Infected subjects with VHB may give strong immunologic response, both to CD4+ and CD+8 which are multispesific and polyclonal cellular to HBV. Inversely, those with chronic infection showed weak or no anti-HBV response.

During HBV acute infection, T helper (Th) response, MCHC-2 CD+4 dependent to multiple epitope of HBcAg/HBeAg are predominant in all patients. Response to envelope Ag HBV is not apparent. What makes the disparity remains unclear because patients who had already vaccinated with HBsAg could induce CD+4 responses which restricted MHC-2 to VHB envelope protein. It is possible that T-cell anti-envelope response had occurs early during primary infection but tolerant or exhausted to high titer viral antigen exposure or improper antigen presentation to immune system. The absence of relative anti-envelope T cell response has important role in controlling viral infection although nucleocapsid MHC-dependent CD+4 involved in immunoregulatory system. By helping B cell to form anti envelope Ab and HBV-specific CTL activation, Th CD+4 may directed early antiviral response. During chronic infection of HBV, strong specific response CD+4 will be exhausted or non responsive. The cause of these molecular changes is not clear yet. CTL is involved in reaction to intracellular pathogen especially virus. It can find and eliminate intracellular virus by viral peptide recognition. The finding of CTL which is specific for HBV infection in peripheral blood and liver tissue in patient with chronic infection although is rare, assumed to be associated with 'pathogenic relation' between indolent CTL, necroinflammatory liver disease and chronic hepatitis B. This is the reason why CTL in HBV is considered as double edge sword. Strong CTL response induces viral clearance; inversely ineffective CTL response may cause hepatocellular damage.

CLASSIFICATION[10]

HBV is divided into several serotypes/genotypes according to geographic distribution. Genotype A is associated with good prognosis and longer survival. Genotype C is associated with more severe course of disease. On the other hand, genotype B is associated with the occurrence of HCC. The mutation affects the core gene. There are 2 gene cores HBcAg and HBeAg. HBcAg forms nucleocapsid which essential for viral replication and formation. HBeAg is synthesized as alternative process of gene core, released into circulation, nonessential for replication or induce productive infection in vivo. HbeAg is used for clinical practice as viral replication index, disease severity, and therapeutic response. It is assumed to have role in HBV life cycle.

HBeAg induces Th_2 response in mice, while HBcAg induces Th_1 response. Th_2 response to HBcAg is predominant compare to Th_1 response to Ag nucleus which causes reduced Th_1-specific HBcAg in vivo. It makes viral persistent. In mice, HBeAg may induce Th_1 response including IFN and other cytokines production needed for viral clearance.

CLINICAL COURSE OF DISEASE

Disease course in HBV infection is determined by interaction between viral replication process and immunologic host response. Other factors that may have role are gender, alcohol or concurrent infection of other hepatitis virus. Final result of HBV infection depends on disease severity at time when replication process of HBV is ceased.[11] Final result of chronic hepatitis B infection seemed to be dependent to length course of infection and liver damage severity during phase 2.[12] Disease course of chronic hepatitis B is classified into 3 categories as follows:

Immune tolerance response: during this phase, HBeAg is positive, serum HBV DNA level is high but there is no clinical symptoms, normal ALT and mild histologic changes. This phase lasts for about 10 to 30 years and during this phase, spontaneous seroconversion of HBeAg is as low as 2% in 3 years period.

Immune clearance phase: HBV replication is reduced, ALT level is elevated and inflammatory activity in the liver is increased. Seroconversion of anti HBe begins with changes of ALT. This phase usually occurs in age 15 to 35 years old.

Low replication phase: HBsAg in serum persists but HBeAg disappear and HBV DNA can only be detected by PCR-assay. It is commonly developed to cirrhosis or HCC.

TREATMENT

Many kinds of drugs had been used for chronic hepatitis B treatment both immunomodulator (IFN-α) and antiviral (lamivudine, adefovir dipivoxil, entecavir, emtricitabine). However, most of them had not shown satisfactory efficacy and only small group of them had been approved for clinical practice.[13] Main goal of treatment is to eliminate or reduce replication and thus, stopped or decreased hepatic necroinflammation.[1,7,9,14] Short term goals of treatment are to reduce the symptoms if there is any clinical symptom, reduce hepatic activity, prevent development of hepatic decompensate, confirm elimination of HBeAg and or DNA with normalization of ALT.[7] Long term treatment goals are to prevent relapse of ALT elevation, specially in patients with hepatic decompensate, progression to cirrhosis and or HCC.[7,13]

A. MONOTHERAPY

Interferon (IFN)α [1,4,7,9,11,15,16]

Interferons have anti viral, anti proliferative, and immunomodulatory effects. It can prevent penetration of virus into hepatocyte and activate viral ribonuclease that suppresses HBV replication. It is also considered to have capability to increased CTL activity, stimulate NK cell activity and increase HLA-1 protein in infected cells. Theoretically, IFN-α is an ideal drug in the treatment of chronic hepatitis. Long term follow-up study had shown IFN-α therapy was beneficial for HBeAg seroconversion, longer survival, prevent cirrhosis and HCC in the responsive group. IFN-α treatment was given in patient with high replication activity state (the presence of HBeAg or HBV DNA in the serum, patient with elevated aminotransferase or evidence of chronic hepatitis B from liver biopsy). Absolute contraindication of giving treatment of IFN-α are psychotic, severe depression, pregnancy and seizure. Relative contra-indications are history of depression, uncontrolled diabetes mellitus, uncontrolled hypertension, retinopathy, psoriasis, thyroiditis, and symptomatic cardiac diseases.[4]

IFN-α is given by subcutaneous injection with recommended dose in adult is 5 mu/day or 10 mu, three times per week. In children it is given 6 mu, three times per week with maximum dose of 10 mu. It is given for 16-24 weeks in patients with positive HBeAg. Patients with negative HBeAg should be treated for at least 12 months. Wong et al reported group of patients whom given IFN-α treatment had higher seroconversion rate (33% vs. 12%) and higher DNA suppression (37% vs. 17%) compare to control group.[2] side effects of IFN-α in early course of treatment is flu-like syndrome. Some

patients had weight loss, bone marrow suppression, at higher risk of sepsis, alopesia, thyroid dysfunction, depression, and psychiatric disorder and need adjustment dose or quit from IFN treatment.[2,17] IFN-α may induce autoimmune phenomenon and more than 50 patient whom had been treated for 4 months had formed auto antibody like anti thyroid, anti nuclear, and anti smooth muscle.[18] Conventional IFN is commonly given 3 times per week for 4-6 months. Other preparation which is under clinical trial is pegylated interferon (Peg IFN-α 2a). Peg IFN-α is additional branch of poliethylene glycol 40 KD in the base of IFN-α 2a. Pharmacokinetics and pharmacodynamics improvements occur due to pegylated process. Phase II ongoing multi centre study had observed 194 naïve patients whom had been given peg IFN-α 2a once a week with dose 90 μg, 180 μg, 270 μg and Roveron 4.5 uA for 24 weeks. All treatment doses were considered effective because they found rapid reduction of HBeAg compare to conventional IFN-α 2a. Decrease of HBV DNA level was less than 1.5 log on 1st week until 4th week and 3.5 log on 24th week (IFN-α 0.76 log and 2.2 log). In the end of 48th week Peg IFN-α 90 μg and 180 μg had shown 2 times higher response rate than conventional IFN-α 2a. Those who had been given dose of 270 μg did not showed good result. In difficult patients (low level of ALT, high HBV DNA level, sign of cirrhosis) showed considerable response as well. Unwanted reactions were not prominent and going back to normal after IFN was stopped. However, there are still many things to consider and more data will be needed before this drug is recommended.[19]

Lamivudine (Epivir HBV, 3TC) [2,4,7,9,13,15,16,20]

Lamivudine is the only direct anti viral agent that had been approved and available in all over the world. Lamivudine is nucleoside analog with potent inhibitory effect on polymerase HBV. However, suppression effect is usually not complete and that is why it would need longer course of therapy. Studies showed that lamivudine was effective for seroconversion of HBeAg, normalization of ALT and histologic improvement in both Asian and Western patients. Lai et al reported improved necroinflammation activity in 56% patients who received 100 mg lamivudine compare to 49% who received 25 mg and 25% who received placebo.[20] Lamivudine had rapid onset of action, so it is highly recommended for patients with hepatic decompensate. Lamivudine had showed satisfactory result in patients with negative HBeAg. Main issue in lamivudine treatment is the occurrence of drug resistant and long response maintenance. Resistant to lamivudine is approximately 15-22% after 1 year lamivudine treatment.[8]

Recommended dose for adult with normal renal function and no HIV infection is 100 mg/day. Recommended dose for children is 3 mg/kg BW/day and maximum dose 100 mg/day. Patients with renal insufficiency should be given less. Patients with HIV infection should be given 150 mg twice daily. In general, lamivudine should be given for 1 year and stopped if it already had 1 year treatment and persistent seroconversion of HBeAg (HBeAg disappear, presence of anti HBe and HBV DNA is not detected by non-PCR method more than 1 single examination at 2-3 months interval). Positive response after cessation of drugs may persist reaching 70-80%. It had been reported that 16% patients had acute exacerbation of HBV infection after lamivudine had been stopped.[21] Dienstag et al, reported histologic response was 52% in patients whom received lamivudine treatment compare to 23% in placebo group. Besides, HBeAg seroconversion was higher in the treatment group than in placebo group (17% vs. 6%).[3] Studies in Asia on lamivudine treatment for 1 year had reported normalization of ALT in 72% cases and 16% HBeAg seroconversion.[22]

YMDD Mutation

After 9-10 months of therapy with lamivudine, it showed there was group of patients who was resistant. This species had undergone mutation of polymerase gene and was called YMDD mutation. Leung had reported incidence was nearly reaching 50% in 3 years.[23] The occurrence of YMDD mutation was sometimes accompanied by the return of HBV DNA, commonly elevated ALT (hepatitis flare) and decompensate condition.[21] Lai reported variant incidence in 67% after observation for 4 years. It appeared that 33% patients with YMDD mutation might still undergo seroconversion of HBeAg and 59% had normal ALT in the end of examination.[24]

Adefovir dipivoxil[2,9,13,14]

Adefovir dipivoxil is active both in vivo and in vitro to lamivudine resistant HBV. It is given for 48 weeks, 10 mg/day (oral), well-tolerated, no significant effect on electrolyte serum and renal function. It is a phosphonate nucleoside analog from monophosphate adenosine which may reduce HBV DNA level in serum to 2-4 log.[8] Chemical name of adefovir dipivoxil is 9{(bis[pivaloxy]metoxy)phosphinyl)metoxy) ethyl)adenine}. In vitro, it is effective in suppress mutant replication which is resistant to lamivudine.

Adefovir is excreted through kidney. Dose more than 10 mg is sometimes associated with nephrotoxicity

indicated by elevation of creatinin level and decrease of serum phosphor. Patient with underlying renal dysfunction who receives adefovir will need more attention if also received cyclosporine, tacrolimus, aminoglycosides, vancomycin and NSAID. Renal function should be monitored during adefovir therapy and if there is decreased renal function, the dose may be adjusted. Drug interaction increases to 23% if adefovir is given concomitantly with ibuprofen 800 mg three times daily. In pregnancy, experimental study on mice showed no toxicity to embryo or no teratogenic effect found with dose as much as 35 mg/kgbw/day. Study on rabbits using dose 20mg/kgbw/day showed the same result. However, trial on pregnant patients had not been done yet. Benefit and risk ratio have to be considered very carefully before giving treatment of adefovir.[25]

A research study had studied comparison between 10 mg and 30 mg of adefovir per day in 515 patients aged 16-55 years old for 1 year. Patients were recruited from 78 centers from all over the world. Inclusion criteria were positive HBeAg at least for 6 months, minimum HBV DNA in serum 1 million copies/ml and elevated ALT 1.2 -10 times from normal value. Prothrombine time was not more than 1 second beyond normal level, albumin level at least 3 mg/dL. Total bilirubin was not more than 2.5 mg/dL, creatinin level was not more than 1.5 mg/dL, and relatively normal peripheral blood examinations. After 48 weeks, patients were treated with adefovir had showed histologic improvement, reduction of HBV DNA, elimination of HBV DNA, normalization of ALT and seroconversion of HbeAg. There were no resistant mutants found at polymerase gene of HBV DNA. It showed that more unwanted reactions seen in patients received 30 mg/day. Thus, dose of 10 mg/day was recommended for long term treatment.[26]

Entecavir (ETV)[2,9]

Entecavir is a deoxyguanine nucleoside analog which is selective inhibitor of HBV replication and selective activity countered HBV. Entecavir is effective for HBV mutant which is resistant to lamivudine and have effect 30 times more potent than lamivudine in cell suppression especially on Hep G2.2.15. Robert A De Man et al had conducted clinical trial with placebo controlled of 42 patients who received entecavir with 4 times dose increment (0.05, 0.1, 0.5, 1 mg).[19] In all patients, there was reduced HBV DNA serum after 4 weeks of therapy. Entecavir inhibited HBV replication through 3 phases:

- Priming/maturation of polymerase HBV DNA
- In reverse transcriptase formation from negative chain of HBV DNA from mRNA pre-genomic.
- Synthesis of positive chain of HBV DNA

Other studies which had compared treatment of entecavir (0.05, 0.1, 0.5 mg) with lamivudine 100 mg indicated entecavir with dose 0.1 and 0.5 mg was better in viral response and HBV DNA reduced and seroconversion of HBeAg after 22 weeks, and decreased ALT (14%) after 24 weeks.

Emtricitabine (Coviracil/FTC)

Emtricitabine is transcriptase inhibitor deoxytidine analog which had been proven to have potent and selective inhibitory activity against HBV and HIV. Chemical name is FTC [(-)-2',3'-dideoxy-5 fluoro-3'-thiacytidine]. Pre-eliminary multicentre study using emricitabine had been conducted in 49 patients (screening from 92 patients) aged 18-55 years old with positive HBsAg for minimum 3 and negative IgM HBV, and ALT level not more than 2 times normal value. Patients who received interferon in the last 3 months, received other antiviral or nucleoside analog for more than 3 months or 60 days during screening period, including those received antiviral therapy, immunomodulatory drug or corticosteroid were excluded.

This study was a cohort study of dose escalation phase I-II. Patients received 25 mg 10 mg (11 patients), 50 mg (8 patients), 100 mg (11 patients), 200 mg (9 patients), and 300 mg (10 patients) for 8 weeks and were observed until the next 28 days after cessation of therapy. HBV DNA level was checked at the beginning and every period of drug therapy. Viral suppression was found in all doses used and well tolerated.[16] It was concluded that further study is needed for treatment of infection. Pharmacokinetics study on emcitarabine reported that viral suppression effect would be more prominent if the starting dose given was at least 100 mg/day.[27]

Tenofovir disoproxil fumarate (TDF).[28,29]

Tenofovir R-9-(2-phosphonyl-methoxypropyl) adenine is an acyclic nucleoside reverse transcriptase inhibitor which had been approved by FDA. It wasusually used for HIV-1 treatment. HIV infected patients were commonly to have concurrently HBV infection. That is why some researchers had tried this drug on HVB infection. In vitro, it can inhibit HBV activity including HBV variant which is known to be lamivudine resistant. The study was conducted for 24 weeks in 6 HIV infected patients with persistent HBV replication although they had received interferon with lamivudine or emcitarabine and had viral load $> 10^6$ copies/ml. Patients were received TDF 300 mg/day orally beside the standard regimen of anti viral therapy. They were observed on 4th, 8th, 12th and 24th week. TDF

was well tolerated during study period. On the 12th week, it was found reduced HBV load in serum 3.1 $\log_{10}$ copies/ml (7.9 ± 0.6 $\log_{10}$ convert to 4.8 ± 1.0 $\log_{10}$ copies/ml), until 24th week HBV load reduced to 3.6 ± 0.4 $\log_{10}$.

Other study was conducted involving 20 homosexual HIV infected patients aged 22-52 years old with positive HBV and HBeAg. Patients received TDF 245 mg (oral) for 52 weeks. Examinations were conducted on 4th, 12th, and 24th week, then it was continued to be checked every 12 weeks. On 24th week, 2 patients showed seroconversion to positive anti HBe, and on 52nd week, 5 patients (25%) had also showed seroconversion. It was concluded from both these studies that TDF was good for positive HBV treatment in HIV positive patients who was resistant to lamivudine.

B. COMBINATION THERAPY [9,20]

Monotherapy after 12 months was usually followed by viral resistance in about 15% of patients per year. Combination therapy has synergistic anti viral effect, reduced the risk of resistance and minimizing toxicity. Combination therapy consists of 2 or more drugs given concurrently. First thing needs to know is that every drug must have been proved well tolerated to give individually. Time of giving drug should be carefully observed, whether these drugs can be given at the same time or one drug at a time and which drug should be given first. Drugs used for combination therapy are as follows:

IFN-α and Lamivudine

IFN-α and lamivudine would be more effective and give seroconversion rate of HBeAg higher than monotherapy. Schalm et al studied 230 patients with chronic HBV infection and reported seroconversion rate of HBeAg on 52nd week was 29% for combination therapy, 19% for IFN-α monotherapy and 18% for lamivudine monotherapy.[20] Lamivudine was given for 52 weeks while IFN-α given for 16 weeks.[30] In combination therapy, lamivudine was given for 24 weeks and IFN-α was given on 16th week.[30] Barbaro et al, reported 94% - 96% from 151 patients showed improvement compare to those who only received monotherapy. Relapse of HBeAg and HBV DNA was found higher in 7% patients for combination therapy and 20% in those whom received monotherapy of lamivudine.[31]

Lamividune and adefovir dipivoxil.[13]

Combination therapy of lamivudine and adefovir dipivoxil had promising result to reduce drug resistance. Use of lamivudine and adefovir were evaluated in 2 studies which were presented in AASLD (American Association for the Study of the Liver) 2001 in lamivudine resistant patients, decompensate cirrhosis or recurrent HBV infection after liver transplantation. Suppression of HBV replication was reduced in all patients and most of them had showed improvement of biochemical and clinical status. Unwanted reactions found were very mild. Clinical improvement indicated that combination therapy is the treatment of choice in patients who have liver disease and need long term therapy.[31]

CONCLUSION

IFN-α has immunomodulator property and is effective to inhibit viral replication and eradicate carrier condition in chronic HBV infection. Lamivudine is oral anti viral drug which has potent inhibition effect but commonly induce drug resistance and acute exacerbation after cessation of therapy.

In the treatment of chronic HBV infection, combination therapy should be considered if there is no sufficient response to monotherapy. To date, the treatment of chronic HBV infection had not showed satisfying result yet. However, ongoing clinical studies have been conducted and may contribute for development in the treatment of chronic HBV.

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