Review Article

Clinical management of hepatitis B virus infection correlated with liver transplantation

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BACKGROUND: **As a radical cure for post-hepatitis B virus (HBV)-related liver cirrhosis and hepatocellular carcinoma, liver transplantation has been applied in many medical centers. Before the use of effective measures, hepatitis B recurrence and the existence of HBsAg(+) donors, patients with hepatitis B-related diseases are contraindicated for liver transplantation. Application of interferon, hepatitis B immunoglobulin (HBIG), and nucleotide analogues (e.g., lamivudine) has made great progress in the clinical care of HBV. However, there are still many shortcomings such as low viral suppression rate, rising expense, and the induction of HBV tyrosine-methionine-aspartate-aspartate (YMDD) mutation. This article systematically reviews the current evidence that immunotherapy, conventional drug combinations, and some special fields of HBV infection correlate with liver transplantation.**

DATA SOURCES: **Studies were identified by searching MEDLINE and PubMed for articles using the keywords "hepatitis B virus", "hepatitis B vaccination", "lamivudine", "adefovir", "entecavir", "tenofovir", "HBV genotype", and "liver transplantation" up to October 2009. Additional papers were identified by a manual search of the references from the key articles.**

RESULTS: **Hepatitis B vaccine and human monoclonal antibody have very good clinical prospects. Compared with traditional therapies, the new medical regimens have many benefits such as boosting viral suppression rate and decreasing medical expenses. The triple therapy for YMDD mutation also has an excellent therapeutic effect and a low barrier to resistance. New nucleos(t)ide analogues (entecavir and tenofovir) eliminate virus more effectively with few adverse reactions, and may replace lamivudine or HBIG in future.**

CONCLUSIONS: **Hepatitis B vaccine needs further large-scale and rigorous randomized controlled trials to confirm its effective dose and injection frequency. Monoclonal antibody is still experimental, and the next step is to carry out the relevant animal and human studies. A consensus standard regimen for the treatment of hepatitis B should be developed.**

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KEY WORDS: **hepatitis B vaccination; hepatitis B immunoglobulin; lamivudine; liver transplantation; adefovir; hepatitis B virus; genotype**

Introduction

Hepatitis B is a viral infection that attacks the liver and can cause both acute and chronic diseases. About 2 billion people worldwide have been infected with the virus and about 350 million live with chronic infection. An estimated number of 600 000 persons die each year from the acute or chronic consequences of hepatitis B.

Liver transplantation is a radical cure for post-hepatitis B virus (HBV)-related cirrhosis and hepatocellular carcinoma. In Japan, the morbidity of post-HBV-related liver cirrhosis is about 13.9%.[1] In China, HBV related diseases is the most common primary reason for liver transplantation (78.6%).[2] Although liver transplantation can alleviate clinical symptoms such as ascites, hepatic encephalopathy, hypoalbuminemia, and infection, the adverse effects of immunosuppressive drugs raise the possibility of HBV recurrence or virus breakthrough.[3] Choosing the right prophylactic drug to control the HBV DNA load at an acceptable level is very important.

Immunotherapy is a promising treatment that can enhance the body's ability to resist viruses. Traditional non-specific immune therapy is a passive one such as HBIG. Then studies have been concentrated on

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the specific immune therapy for stimulating active immunity-vaccines. The development of new vaccines that stimulate an effective immune response when patients receive an organ transplant is a hot topic. Recently, Pan et al[4] synthesized engineered mAbs that showed inhibition of HBV *in vitro*.

Various monotherapies and combinations have been developed for the treatment of hepatitis B.[5, 6] These drugs have played important therapeutic roles, and they also have inherent disadvantages such as adverse reactions, hepatitis B recurrence, and long-term drug-resistant strains. Viral resistance mechanisms and the pharmacoeconomics of combination therapy have been reported.[7]

Immunotherapy

Hepatitis B vaccination: dose and phase?

Inducing an active immune response against the hepatitis B surface antigen (HBsAg) leads to continuous secretion of specific antibodies. The vaccine is given in either three or four separate doses as part of the existing routine immunization schedule. The safe anti-HBs titer for continuous prevention of HBV reinfection varies in some studies. Relatively low seroconversion rates and serum anti-HBs concentrations are reported among chronic HBV-infected liver transplantation recipients; only a minority of vaccines may have stable antibody levels >100 IU/L.[8] In the past, anti-HBs-positive individuals (seropositivity: anti-HBs titer of >10 IU/L) have always been considered safe to receive orthotopic liver transplantation for non-HBV-related diseases. Five of nine *de novo* HBV-infected patients were anti-HBs positive before orthotopic liver transplantation.[9] So, for prevention of *de novo* HBV infection after transplantation, the protective anti-HBs titer should be >200 IU/L.[10]

It has been reported that the response rate to HBV vaccine is significantly lower in patients with liver cirrhosis, immunocompromised patients, or organ transplant recipients.[8] When discussing immune status including T-cell and B-cell activity with response rate, Tahara et al[11] found that T-cell interactions which lead to an effective immune response to hepatitis B vaccination can cause activation of anti-HBsAg-specific T cells and suppression of anti-donor-specific T cells. Patients showing a donor-specific hyporesponse with a well-maintained response to a third-party (exogenous) stimulus always have a sustained immune response to the vaccine. Another study on T-cell immunity found that in 12 orthotopic liver transplantation recipients with HBV recurrence, the HBV-specific T-cell immunity was enhanced to a level comparable to that of patients with chronic hepatitis B, and the level was dependent on the serum viral load. Thus this raises an interesting question whether the higher response in the

Table. Comparison of four studies of hepatitis B vaccination

Author*	Dose (μg)	Time of vaccine (weeks)	Combination	Patient characteristics	Results (HBsAb titer and response rate)	Effect factors
Yamashiki et al (2c)[14]	40	0, 4, 8, 24, 28, 32	HBIG	CHB underwent LT (*n*=18), recipients of HBcAb(+) donor organs (*n*=2)	48 weeks: HBsAb titer above 500 IU/ml (*n*=0), 300-500 IU/ml (*n*=2), 100-300 IU/ml (*n*=16)	Not included
Pascasio et al (3b)[15]	40	0, 4, 8, 24	None	Cirrhotic patients (*n*=157), nonresponders (*n*=17)	The response rates were: 1 dose, 40% (2/5); 2 doses, 0% (0/7); 3 doses, 32.7% (16/49); and 4 doses, 31.3% (30/96) of patients. The median anti-HBs titer was 45 IU/L (11-620 IU/L).	Diabetes(-)#
Bonazzi et al (3b)[16]	40	0, 4, 24	None	Cirrhotic patients (*n*=43)	41% of responders had anti-HBs titers above 1000 IU/ml, 35% between 100 and 1000 IU/ml and 24% between 10 and 100 IU/ml.	No variable was observed
Jin et al (2c)[17]	40	0, 4, 8, 24	HBIG+lamivudine	HBV-related ESLD post LT (*n*=13)	The median anti-HBs titer was 91 IU/L (16-199 IU/L). 7 patients developed higher serum titers of anti-HBs, 2 patients developed a 100 IU/L increase, and 4 patients' base levels were doubled.	Not included

*: The Roman numerals in the bracket just following the author are the levels of evidence of papers based on Oxford Centre for Evidence-based Medicine Levels of Evidence(March 2009); #: Diabetes is a negative variable correlated with vaccine response. CHB: chronic hepatitis B; ESLD: end-stage liver disease; LT: liver transplantation.

research of Tahara et al is really due to the donor-specific hyporesponse or just to the activity of anti-HBsAg-specific T cells or both. Schumann et al[12] demonstrated that HBV-specific humoral and cellular immunity can be transferred by liver transplantation after vaccination of the donor. The transfer of B-cell and T-cell immunity correlates with the magnitude of the immune responses in the donor.

The response rate of liver transplantation candidates (with HBV-unrelated liver failure) to recombinant hepatitis B vaccination varies from 16% to 62%.[13] Many variables are associated with the response rate, the most important being the injection frequency and dose per injection. The Table shows four different studies of hepatitis B vaccination. Although these studies may be incompletely randomized or lack proper controls they show that 3-4 doses (40 μg), which can stimulate the necessarily response rate (30%-41%), are optimal for vaccination. But the HBsAb titer of responders varies a lot. Larger randomized controlled trials with good quality controls and design will provide more distinct answers about the dose, phase and response rate of hepatitis B vaccination.

In special patients, the existing routine immunization schedules may not be equally effective as in normal people. Yamashiki et al[14] investigated 18 patients who underwent liver transplantation for chronic hepatitis B and 2 non-HBV-infected patients who received hepatitis B core antibody (HBcAb)-positive donor organs; double-dose double-phase use of second-generation recombinant vaccine was not effective in preventing hepatitis B recurrence in the study population. These populations should be targeted for a conventional vaccine regimen, and different approaches such as strong adjuvant or pre-S containing protein should be further tested.

Vaccination also shows differences in sex, both in adult and pediatric liver transplantation groups. Girls respond with higher anti-HBs titres than boys, as do women.[18, 19] It has become an interesting controversy whether the treatment is individualized to different ethnicities or groups of people. Ni et al[19] found that more than half of the children who were primarily vaccinated with HBV vaccines maintained adequate anti-HBs titers 1 year later after liver transplantation. All consecutive patients maintain a certain degree of cellular immune response irrespective of their anti-HBs status after liver transplantation. We expect that one or more doses of booster may help children who receive transplantation to develop protective response to anti-HBs.

Human mAb: a novel approach?

High specificity monoclonal antibodies to pathogens such as human papilloma virus have greatly expanded therapeutic methodology. Genetically engineered mAbs specific to the surface antigens of HBV would be a good alternative for the immunoprophylaxis of HBV infection.[20] Thus Pan et al[4] cloned the gene of a high Fab-affinity antibody from human peripheral blood and constructed Fab antibody rAAV-HB. After evaluating the activity of antibody hepatitis B in tree shrews treated with intramuscular injection of rAAV-HB and *in vitro* experiments, they concluded that human antibody will be useful for the immunoprophylaxis of HBV infection, but this needs further study in human experiments. The safety and efficiency of transgenic drugs is controversial, which may restrict the use of engineered monoclonal antibodies.

Drug regimens

HBIG and lamivudine combination: low-dose intramuscular or high-dose intravenous HBIG?

The HBIG (10 000 IU per month) and lamivudine regimen used to be the gold standard for prophylaxis against HBV recurrence after liver transplant. This therapy reduces the risk of recurrence to less than 5% at 5 years.[21] However, the cost of HBIG has driven people to investigate a low-dose of intramuscular HBIG (400-800 IU per month) and lamivudine in combination. This combination can achieve the same prophylaxis effect at a lower cost.[22] In Tashiro's research,[23] although two patients were preoperatively HBV DNA-positive shown by a transcription-mediated amplification assay method, all 14 patients receiving a high dose (10 000 IU/day) of HBIG and lamivudine in combination postoperatively became HBV-DNA-negative and HBsAg-negative.

In Chinese liver transplant patients, the efficacy of HBIG was found to be associated with human leukocyte Fcγ receptor 3A gene polymorphisms (at nucleotide site 559). Among the 559G carrier group (n=42, 54.5%), the risk of HBV recurrence was 9.5%, and the 1- and 2-year recurrence-free survival rates were 95.2% and 88.7%, respectively. In the 559G noncarrier group (n=35, 45.5%), the risk of HBV recurrence was 28.6%, and the 1- and 2-year recurrence-free survival rates were 74.3% and 69.3%. Detecting FCGR3A genotypes can be a clinical reference for treatment before HBIG administration.[24]

Hooman et al[25] pointed out that administration of intravenous HBIG (2000 IU per six weeks) and intramuscular administration of HBIG (2000 IU per six weeks) are equally effective with antibody against hepatitis B surface antigen (anti-HBs) in pharmacokinetics. Intramuscular HBIG may not be dose-saving; however, it may be cost-

effective if the price per unit of intramuscular HBIG is lower. Individualized dosing intervals should be further evaluated as a cost-effective alternative to fixed dose schemes.

Saab et al[26] compared prophylaxis with lamivudine and adefovir (strategy 1), with intramuscular HBIG and lamivudine (strategy 2) with the addition of adefovir in patients who subsequently developed hepatitis B recurrence. The medical costs for strategies 1 and 2 after 10 years of therapy were $151819 and $166246, respectively, and the cost saving was $14427. They developed a Markov model to provide pharmacoeconomic support for the use of strategy 1 as first-line therapy in hepatitis B prophylaxis in liver transplant recipients 1 year after transplantation. Strategy 1 not only decreased the total fee for preventing hepatitis B after liver transplantation, but also improved the quality of life. Administration of HBIG requires frequent blood tests to assess antibody titers. On the other hand, adefovir is an oral medication with rare adverse effects and less demand for frequent monitoring.

High-dose HBIG during the ahepatic period and in the early stage of post transplantation can fulfill the treatment target as a long-term lamivudine therapy before liver transplantation. Long-term preoperative lamivudine treatment may result in an earlier HBV mutation in YMDD and increase the HBV recurrence rate and risk in the first year after transplantation.[27] Yilmaz et al[28] found that recurrence can be prevented in E-antigen-negative patients with HBIG alone or in E-antigen-positive patients with a combination of HBIG and an anti-viral agent. Eight out of fifteen E-antigen-positive patients who received HBIG alone developed recurrence after a mean of 17 months. As long as the anti-HBV surface remained detectable, no absolute minimum serum level appeared to lead to recurrent HBV. But the question is raised whether this combination or use of HBIG alone should be continued within 1 year after operation.

Polyvalent immunoglobulin can cause nephrotoxicity. Pathologic examination of the kidneys generally reveals changes typical of osmotic nephrosis. The inappropriate use of HBIG can increase the risk of renal dysfunction, particularly in combination with nephrotoxic drugs.[29]

Lamivudine and adefovir dipivoxil regimen: effective and easy to get

Lamivudine and adefovir represent two different classes of anti-HBV agents (L-nucleoside and acyclic phosphonate) with different mechanisms of action, and there is no cross-resistance between them. Their combination greatly reduces the risk of subsequent adefovir resistance in nontransplantation patients.[30] Prophylaxis combined with adefovir/lamivudine therapy without the use of long-term HBIG is effective and well tolerated.[31] Meanwhile we cannot exclude the possibility that with a prolonged follow-up, some patients may experience viral breakthrough due to the appearance of lamivudine/adefovir resistance.[5]

Before liver transplantation, lamivudine was proposed to be down-graded from the first to second-line therapy. In contrast, adefovir dipivoxil has been approved not only as the first-line therapy but also as rescue therapy for patients with lamivudine resistance.[32] A retrospective cohort study evaluated the safety and efficacy of adefovir in 68 elderly and cirrhotic patients with lamivudine-resistant chronic hepatitis B, among whom 75.4% received a combination treatment with lamivudine and adefovir for a median duration of 12.6 months; the remaining patients received adefovir overlapping with lamivudine treatment for a median duration of 7.9 months. At the end of the follow-up, 41.2% of the patients had undetectable HBV DNA ($\leqslant$2000 copies/ml) with a median reduction of lg3.4 copies/ml. No resistance mutations and no significant side effects were observed.[33] Even though no combination treatment can cover all the possible mutation strains, we focus on reducing the resistance as much as possible to get a good prognosis.

A seven-year follow-up study of 24 patients showed that HBV recurrence developed in 7 patients with cumulative probabilities of 8%, 13%, 28%, 35%, 35%, and 49% in 1, 2, 3, 4, 5, and 6 years. Four patients had rtM204I mutation, and in 3 of them HBV DNA levels were too low for sequencing. After use of lamivudine followed by adefovir salvage for 150 weeks (91-193), 6 (86%) patients had normal ALT levels. HBV DNA was undetected in 2 (29%) patients, 100-1000 copies/ml in 2 (29%) and 10 000-100 000 copies/ml in 3 (43%) on the last visit. No genotypic resistance to adefovir was detected,[34] showing that lamivudine followed by adefovir salvage is effective for prophylaxis of recurrence of HBV for up to 7 years after liver transplantation.

Management of YMDD mutant: lamivudine, adefovir and HBIG triple therapy

YMDD mutation is common in the application of lamivudine in treating HBV. In 183 adult liver transplantation patients who lived more than 6 months and were followed up for 14.6 months, the rate of YMDD mutation in the lamivudine group was 8.49% (9/106), markedly higher than that in the lamivudine+HBIG group (1.30%, 1/77; P=0.035). The patients with YMDD

mutation improved after treatment with adefovir.[35]

In patients with YMDD mutation at the time of transplantation, combined use of HBIG and lamivudine is not consistently successful in preventing reinfection. In this situation, the addition of another antiviral agent combating the drug-resistant virus (i.e., adefovir, tenofovir, or entecavir) would be expected to further reduce the risk of prophylaxis failure.[36]

As described in a ten-year study from Ikegami et al,[37] patients with YMDD mutation (9 of 29 patients), except an HBsAg-positive donor, were successfully protected by the triple therapy of lamivudine, adefovir, and HBIG. No graft loss was due to the recurrence of HBV. YMDD mutation should be closely monitored during lamivudine treatment.[38]

Other oral nucleos(t)ide analogues: entecavir and tenofovir

Entecavir is a guanosine nucleotide analogue. It is a new, highly potent antiviral agent; phase Ⅱ and Ⅲ studies have demonstrated this drug to be superior to placebo and lamivudine in patients with chronic HBV.[39] Because of the low resistance barrier, it used to be a substitute for lamivudine-resistant patients. Kurashige et al[40] recommended that lamivudine-to-entecavir switching treatment may be suitable in chronic hepatitis B patients without evidence of lamivudine resistance during the preceding lamivudine treatment with great attention to the emergence of entecavir-resistance.

Kamar et al[41] reported that 10 male transplant patients with chronic HBV infection who were adefovir- (n=9) or lamivudine-resistant (n=1) were given entecavir at 0.5 to 1 mg/d. All patients were HBsAg-positive. After a median follow-up of 16.5 months, entecavir therapy reduced the HBV DNA viral load from lg3.86 (lg2.71-lg6.46) copies/ml at baseline to lg2.94 (lg2.15-lg4) copies/ml at the last follow-up (P=0.004). The host biological response was better in kidney transplant patients than in liver transplant patients because HBV has a liver tropism which may be more resistant and more aggressive in a transplanted liver than in a native one.[41] This study showed good results of entecavir in treating kidney or liver transplant patients, which may be used in treatment of liver-kidney transplantation patients.

Tenofovir is an acyclic nucleotide analog, reverse transcriptase inhibitor.[42] Zhu et al[43] compared different regimens of tenofovir with lamivudine, entecavir, and adefovir. They found that of combinations lamivudine+tenofovir, entecavir+tenofovir, and adefovir+tenofovir showed additive anti-HBV effects *in vitro*. This supports the use of tenofovir as a component in combination regimens with currently available anti-HBV nucleoside analogues.

Benefits and risks of combination therapy

Many reports describe the benefits and risks of hepatitis B drug treatment. This section just mentions some special points of liver transplantation. Combination therapy for hepatitis B is recommended in specific patients: those who have undergone liver transplantation, those with decompensated cirrhosis, those coinfected with human immunodeficiency virus and HBV who are on antiretroviral therapy, and those with drug-resistant HBV infection.[44] In successful antiviral combination therapy, different drug regimens may cover major virus mutation pathways to minimize possible drug resistance. However, investigators still find many different mutations in response to the first line drugs such as lamivudine with rtM204V, rtL180M, and rtS202G mutations.[40] These mutations may cause virus recurrence and lead to transplant failure. Thus it is important to monitor the status of patients during therapy. Monitoring of treatment response includes tests for serum aminotransferase level, HBV DNA level, hepatitis B e antigen (HBeAg) and antibody (anti-HBe), hepatitis B surface antigen (HBsAg) or antibody (anti-HBs), and liver histology.[45] Early discovery of possible drug resistance may contribute to a good prognosis of liver transplantation.

Genetic factors and drug therapy: individual treatment

Eight distinct genotypes of HBV A to H have been identified, each having a characteristic geographic distribution.[46, 47] Each genotype can be divided into many subtypes like B1-B4, and C1-C4. In China, B2 and C2 predominate.[48] Genotype can effect graft survival rate and the cumulative rate of viral breakthrough. Lo et al[49] found that genotype B patients have more pre-transplant acute flare, poorer liver functions, and higher end-stage liver disease scores. Fewer genotype B patients have HBeAg (13% vs. 32%; P=0.017). The 3-year graft survival rate is 83% for genotype B and 89% for genotype C (P=0.2). The graft survival due to lamivudine-resistant mutation at 3 years is 4% for genotype B and 21% for genotype C (P=0.017). Liver biopsy after viral breakthrough showed recurrent hepatitis B in 7 of 10 genotype C patients.

Gene polymorphism also contributes to host immune behavior to HBV and drugs, such as mutations of the gene coding for the major hydrophilic region of HBsAg may be associated with anti-HBs immunoglobulins or vaccine escape.[50] In Chinese liver transplantation, the organ recipients with CTLA-4 +49 GG genotype have a reduced risk (6.67%, n=11) of HBV recurrence compared

with non-CTLA-4 +49 GG-carrying individuals (20.7%) (relative risk 3.098; P=0.032).[51]

After ending of the human genome project, the concept of molecular medicine has emerged. The evidence mentioned above can lead to early diagnosis and genetic prediction of HBV infection or recurrence. Before prescribing a drug in future we may review the genetic characteristics of a patient and decide the best choice of therapy.

In conclusion, further research is needed to provide evidence-based recommendations about optimal antiviral therapy in adults with chronic hepatitis B infection. Monoclonal antibodies are still in the experimental stage, and the next step is taken to do relevant animal and human studies. A consensus on a standard regimen for the treatment of hepatitis B should be achieved.

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