Review Article

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Prevention of Hepatitis B Virus Reactivation in Kidney Transplant Recipients

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ABSTRACT

BACKGROUND AND OBJECTIVE: Hepatitis B virus (HBV) reactivation is a major risk factor for hepatic dysfunction, acute or chronic hepatitis, cirrhosis, or hepatocellular carcinoma after kidney transplantation (KTP). The present article summarizes some of published articles about prevention of HBV reactivation in renal transplant recipients

METHODS: Many articles published in English language as full-text manuscripts reviewed in a variety of sources such as Scopus, Pub Med and Google Scholar with key words of hepatitis B and kidney transplantation to collect current data about this issue.

FINDINGS: The risk of reactivation of HBV followingKTP is related to the status of serologic markers of HBV at the time of KTP.KTP candidate patients who are hepatitis B surface antigen (HBsAg) positivehave higher risk for reactivation especially those who are hepatitis B e antibody positive or have high levels of HBV DNA in serum. Lamivudine has been most extensively used for prevention of HBV reactivation, but it is associated with a high rate of drug resistance.It seems that the optimal antiviral agent for prevention of HBV reactivation is entecavir which is associated with the lowest risk of drug resistance,however lamivudine-resistant HBV is less sensitive to entecavir. The preferred antiviral agent for lamivudine-resistant HBV is tenofovir which should be added to lamivudine rather than stopping lamivudine. It is reported that combination therapy in this sitting may reduce the development of resistance to the second drug.

CONCLUSION: There is sufficient evidence to recommend routine antiviral prophylaxis for all HBsAg-positive patients who are undergoing kidney transplantation.

KEY WORDS: *Hepatitis B, Kidney Transplantation, Entecavir, Tenofovir.*

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Introduction

Hepatitis B virus (HBV) infection can lead to life-threatening diseases such as severe or chronic hepatitis, cirrhosis, and hepatic cancer (hepatocellular carcinoma). Although effective measures have been taken for the management of this condition, HBV remains endemic in many parts of the world, and more than 350 million people have been affected, worldwide (1-5). Chronic renal insufficiency is a progressive and irreversible condition, causing damage to the kidneys (6-14). This condition can progress into chronic renal failure, which can be fatal without dialysis or kidney transplantation (15, 16).

Overall, hemodialysis is regarded as the most common treatment option for advanced and permanent renal failure (17-26). According to the literature, HBV infection plays a relatively minor role in the survival of hemodialysis patients (27). Based on previous studies, the prevalence of HBV infection among dialysis patients is proportional to its positive rate in the society. The prevalence of this infection has been estimated at 1% in the United States, 5.9% in Italy, 12% in Brazil, 1.3-14.6% in Asia-Pacific countries, and 1.15-7% in Iran.

In endemic areas, most adult dialysis patients are chronic carriers of the virus, who have been infected in early childhood. In contrast, in non-endemic regions, this infection often appears during adulthood (28-35). Symptoms of severe HBV infection in dialysis patients are extremely variable and most cases are asymptomatic or exhibit mild clinical symptoms. Moreover, in these patients, the level of serum transaminase is within the normal range or slightly increased.

Compared to healthy individuals, patients with renal insufficiency are more prone to chronic HBV infection. Also, there is an 80% possibility that dialysis patients become chronic carriers of the virus after an episode of acute HBV infection (36-39). Normally, kidney transplant is performed in cases presenting with renal failure (particularly those in the final stages of the disease) (40-45). Based on the majority of conducted studies, symptoms of HBV infection are relatively minor among dialysis patients, and no significant differences have been observed regarding the morbidity or mortality of HBsAg-positive and HBsAg-negative patients (29, 46-48). However, asymptomatic patients who are carriers of the virus during dialysis are at risk of virus reactivation upon kidney transplant and major hepatic complications after the procedure. If the symptoms of virus reactivation appear shortly after kidney transplantation, the risk of severe and life-threatening complications increases. Although HBV infection is a relatively benign clinical condition among dialysis patients, it is the most important factor leading to liver dysfunction after kidney transplant (38, 39). Considering the important role of this infection in kidney transplant, in this review article, we aimed to discuss the risk factors and preventive measures against HBV reactivation following kidney transplantation.

Methods

In this review study, Google Scholar, PubMed, SID, and MagIran databases were searched, using a combination of the following keywords: “HBV reactivation" and "kidney transplantation".

Results

Risk factors for HBV reactivation: HBV reactivation following kidney transplantation refers to the measurable level of HBV DNA, which was formerly indeterminate in HBsAg-positive patients. Also, in cases with measurable HBV DNA levels, reactivation occurs when HBV DNA level rises by more than one to two logs.

In HBsAg-negative and anti-HBc-positive patients, virus reactivation occurs when HBsAg turns positive or HBV DNA level in the serum becomes measurable (49-55). In patients with a prior history of infection, risk of HBV reactivation depends on the serological and virological markers of HBV at the time of kidney transplantation. HBsAg-positive patients have a higher risk of virus reactivation, compared to HBsAg-negative and anti-HBc-positive cases.

Also, among HBsAg-positive patients, those with higher levels of HBV DNA in the serum are at a greater risk of HBV reactivation. However, HBV reactivation may also occur in patients with indeterminate HBV DNA levels in the serum and negative HBeAg before kidney transplantation.

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However, HBV reactivation rarely occurs in HBsAg-negative and anti-HBc-positive cases (50-53).

Prevention of virus reactivation and replication after kidney transplantation in HBsAg-positive patients: It is recommended that HBsAg-positive patients who are candidates for kidney transplant be treated with antiviral drugs as a preventive measure. Previous research indicates that antiviral drugs can be effective in the prevention of HBV reactivation in non-transplant candidates, receiving immunosuppressive drugs (55-57).

In a study by Loomba and colleagues, 275 chemotherapeutic patients, treated with lamivudine, had a lower risk of virus reactivation, compared to the control group which did not receive lamivudine. In the mentioned study, lamivudine was well-tolerated and induced no side–effects in patients (56). According to the literature, anti-viral treatment could be more effective if initiated before the rise in serum transaminase level or prior to the occurrence of liver dysfunction.

In a study by Han and colleagues on kidney transplant recipients, serum transaminase reduced to the normal level and DNA HBV disappeared in all six patients treated with lamivudine within one month after the onset of treatment. However, three months later, while patients were still receiving lamivudine, liver biopsy indicated severe and chronic hepatitis in four patients, fibrosing cholestatic hepatitis in one patient, and cirrhosis in one patient. On the contrary, among 10 patients who had used lamivudine as a preventive measure, only one case of disease progress was reported (55).

Nucleoside or nucleotide analogues: Lamivudine, which is an oral nucleoside analogue interfering with hepatitis B virus reverse transcriptase, has been used as a prophylactic agent for kidney transplant patients in the majority of studies (55, 56). However, the most important factor inhibiting the administration of lamivudine in transplant and non-transplant patients is the appearance of virus variants during treatment, which show resistance to the drug; in fact, such variants become more prominent as the treatment continues. In a previous study, nearly 15%, 30%, and 50% of patients showed drug resistance after one, two, and three years of treatment with lamivudine, respectively, which could result in the progress of hepatic disease (44-56).

Other effective antiviral agents include adefovir, entecavir, telbivudine, and tenofovir (44-56). Entecavir, telbivudine, and tenofovir, followed by lamivudine and adefovir, are more effective than others. In terms of drug resistance, entecavir and tenofovir, followed by adefovir, telbivudine, and lamivudine, seem to induce the lowest resistance. Therefore, among the mentioned agents, the highest level of resistance can be attributed to lamivudine and telbivudine (44-56). Considering the fact that entecavir is an effective agent, which induces low levels of drug resistance (despite long-term use), it can be effectively administered for kidney transplant patients. In this regard, according to a previous study, after five years of treatment, rate of drug resistance was estimated at 1%. Moreover, it should be noted that entecavir is not a nephrotoxic drug, unlike adefovir or tenofovir. Therefore, use of this agent is suggested as a preventive measure against virus reactivation in both prophylactic and preemptive approaches.

In addition, entecavir is recommended for the treatment of patients not receiving lamivudine for virus reactivation. However, if the patient experiences drug resistance during lamivudine treatment, entecavir administration is not suggested since patients with lamivudine-resistant HBV are less sensitive to entecavir, even if they are responsive to this agent (49-56). Although higher doses of entecavir have been used in multiple studies, resistance to entecavir is greater in patients unresponsive to lamivudine, compared to cases not receiving lamivudine. Therefore, administration of tenofovir or adefovir is preferable for patients with drug resistance, caused by the use of lamivudine.

It should be noted that tenofovir is preferred to adefovir in countries where tenofovir is accessible, since adefovir exhibits weaker antiviral properties and is associated with nephrotoxic risks (31, 40-56). In a previous study, patients who used lamivudine as a prophylactic treatment and consequently showed signs of drug resistance were suggested to use tenofovir or adefovir, along with lamivudine. According to the literature, if lamivudine is used concomitantly with tenofovir or adefovir, the risk of drug resistance to the second agent is reduced (23, 40).

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Based on previous reports, kidney transplant recipients are not recommended to use interferon alfa. On one hand, antiviral effects of this agent are insignificant for patients receiving immunosuppressive drugs, and on the other hand, this drug may lead to major transplant rejection. Furthermore, the five mentioned antiviral drugs are excreted through the kidneys; therefore, it is necessary to set the dosage, based on renal function in patients with renal failure (40).

HBsAg-negative and anti-HBc-positive patients: HBsAg-negative and anti-HBc-positive patients are less likely to experience virus reactivation after kidney transplantation, compared to HBsAg-positive cases. According to the literature, we have no evidence to substantiate routine prophylactic administration of antiviral drugs for these patients (40); however, these patients need to be examined in terms of virus reactivation.

Most physicians only rely on periodical alanine aminotransferase (ALT) examinations, and HBV DNA level is measured only if ALT level is increased. However, some physicians regularly evaluate HBV DNA level and prescribe preemptive antiviral treatments, based on the HBV DNA level. Also, some specialists examine HBV DNA level prior to kidney transplantation and prescribe prophylactic treatments for patients with positive HBV DNA.

It should be noted that while the majority of patients have measurable levels of HBV DNA in the liver, in the minority (less than 5%), HBV DNA is measurable in the serum (40).

Discussion

Generally, there are two prophylactic and preemptive approaches for the prevention of HBV reactivation. In the prophylactic approach, antiviral drugs are administrated for patients who are at risk of HBV reactivation before or immediately after kidney transplantation. In the preemptive approach, the recipients are periodically monitored with regard to viremia, using polymerase chain reaction. The patients are monitored in terms of viremia at least once a month in the first year after kidney transplant and then every six months. Treatment should be promptly initiated if HBV DNA, which was formerly immeasurable, is detected in the patient's serum (55, 56). In terms of clinical prognosis and patient survival, both prophylactic and preemptive approaches are preferred to the salvage method, which is initiated after the onset of liver dysfunction (52-56). Research on non-transplant patients receiving chemotherapy showed that the prophylactic approach is preferred to both salvage and preemptive approaches (23).

In a previous study, 30 HBsAg-positive patients with lymphoma were prescribed 100 mg of lamivudine on a daily basis prior to chemotherapy or after the appearance of serological markers of HBV reactivation. As the findings revealed, virus reactivation was reported in 0% of cases in the first group and 53% of patients in the second group (23). According to the literature, all kidney transplant candidates with positive HBsAg are recommended to receive prophylactic antiretroviral therapy before or during surgery, regardless of the HBeAg status or serum HBV DNA level. This recommendation is based on the limited ability of examinations in predicting virus reactivation in patients after kidney transplantation.

On the other hand, the preemptive approach is a convenient alternative, particularly in patients with immeasurable HBV DNA levels before kidney transplant. This approach requires regular evaluation of HBV DNA level which is not simply accessible in many patients. By the application of preemptive method, antiviral therapy should be commenced if HBV DNA level is measurable or increased (49-56).

Duration of treatment with antiviral drugs: There is no consensus regarding the duration of antiviral therapy. In non-immunocompromised individuals, antiviral treatment is discontinued as soon as seroconversion is observed. However, there is not enough information at hand to determine whether this approach is effective in immunocompromised patients or kidney transplant recipients. Therefore, antiviral therapy is suggested to continue for at least one to two years after kidney transplant. Also, this method is advisable for patients receiving strong immunosuppressive agents due to acute kidney rejection; however, in such cases, most specialists suggest the lifelong use of antiviral agents. In kidney transplant recipients with negative HBeAg and indeterminate HBV DNA level before transplantation,

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antiviral agents can be discontinued as immunosuppressive drugs reduce to the minimum level. As soon as antiviral drugs are discontinued, the patient should be periodically (within short intervals) examined regarding virus reactivation; antiviral drugs are prescribed if there is evidence of virus reactivation (40). Tenofovir is the most favorable antiviral drug for patients with lamivudine-resistant HBV infection. Concomitant use of lamivudine and tenofovir is preferred to lamivudine discontinuation; in fact, this type of therapy can reduce resistance to the second agent.

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