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MINIREVIEWS

Hepatitis B in renal transplant patients

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Abstract

Hepatitis B virus (HBV) poses a significant challenge for both dialysis patients and kidney transplant recipients despite its decreasing rates, especially in developed countries. The best preventive method is vaccination. Patients with chronic renal disease should ideally be vaccinated prior to dialysis, otherwise, reinforced vaccination practices and close antibody titer monitoring should be applied while on dialysis. HBV infected dialysis patients who are renal transplant candidates must be thoroughly examined by HBV-DNA, and liver enzyme testing and by liver biopsy. When needed, one must consider treating patients with tenofovir or entecavir rather than lamivudine. Depending on the cirrhosis stage, dialysis patients are eligible transplant recipients for either a combined kidney-liver procedure in the case of decompensated cirrhosis or a lone kidney transplantation since even compensated cirrhosis after sustained viral responders is no longer considered an absolute contraindication. Nucleoside analogues have led to improved transplantation outcomes with both long-term patient and graft survival rates nearing those of HBsAg(-) recipients. Moreover, in the cases of immunized HBsAg(-) potential recipients with concurrent prophylaxis, we are enabled today to safely use renal grafts from both HBsAg(+) and HBsAg(-)/anti-HBc(+) donors. In so doing, we avoid unnecessary organ discarding. Universal prophylaxis with entecavir is recommended in HBV kidney recipients and should start perioperatively. One of the most important issues in HBV(+) kidney transplantation is the duration of antiviral prophylaxis. In the absence of robust data, it seems that prophylactic treatment may be discontinued in selected stable, low-risk recipients during maintenance immunosuppression and should be reintroduced when the immune status is altered. All immunosuppressive agents in kidney transplantation can be used in HBV(+) recipients. Immunosuppression is intimately associated with increased viral replication; thus it is important to minimize the total immunosuppression burden long term.

Key words: Hepatitis B virus (+) donor; Hepatitis B virus (+) recipient; Renal transplantation; Viral reactivation; Immunosuppression; Nucleoside analogues; Antiviral discontinuation; Antiviral prophylaxis; Hepatitis B

Core tip: Though decreasing, hepatitis B still remains a considerable problem, especially in high-risk patient populations as kidney transplant recipients. The widespread use of new antivirals and the introduction of universal prophylaxis immediately after transplantation have changed the picture in hepatitis B virus (HBV) (+) transplantation. Long term survival rates of HBV(+) recipients are approaching those of HBV(-), altering HBV(+) kidney transplantation from a "high risk" procedure into routine practice. Furthermore, accumulating evidence confirms the safety of transplantation from HBsAg(+) donors into immunized recipients. All immunosuppressants can be used in HBV(+) transplantation and total immunosuppression must be kept at the lowest possible levels long term.

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HEPATITIS B PREVALENCE AND PREVENTION IN HEMODIALYSIS PATIENTS

Acute and chronic hepatitis are caused by a double stranded DNA type of virus, hepatitis B virus (HBV). Although a safe and effective vaccine has been available for at least twenty years now, infection of HBV remains an enormous problem of public health worldwide[1].

Because of increased skin breaching, significant exposure to blood products, the sharing of dialysis machines, the nature of the dialysis process that allows great access to the bloodstream and underlying immunodeficiency problems, hemodialysis patients are at a greater risk for HBV infection. Fortunately, a number of prevention measures have in the last thirty years effectively resulted in the significant reduction of HBV infection incidence amongst hemodialysis patients. These include but are not limited to stricter adherence to general hygiene rules, mandatory separation of these patients during dialysis, aggressive vaccination protocols as well as erythropoietin use. However, hepatitis B prevalence remains a challenge in dialysis[2]. USRDS data indicates that 1% of dialysis patients tested positive for hepatitis B surface antigen (HBsAg) while in a registry study of Asian-Pacific countries the prevalence of HBsAg in hemodialysis populations ranged from 1.3% to 14.6%[3,4]. In general the incidence of HBsAg positivity among dialysis patients ranges from 0%-7% in low-prevalence countries to 10%-20% in endemic areas.

As in most public health challenges, immunization is the most critical move in preventing HBV infection. It is preferable that chronic kidney disease patients are vaccinated at an early stage and certainly prior to going on dialysis, because vaccine immunogenicity is higher in the general population in comparison to dialysis patients (90% *vs* 70%). Still, dialysis patients should also be vaccinated against HBV infection and have an annual test regarding their hepatitis B antibody (anti-HBs) titer. If it is lower than 10 IU/mL, an intensified protocol should be followed vis a vis a booster vaccine dose should be administered. Such protocols have shown very good responses in hemodialysis patients[5].

HBV EVALUATION IN THE PRETRANSPLANTATION SETTING

HBsAg (+) kidney transplant candidate

All dialysis patients should be routinely checked for HBsAg. In case of seropositivity, additional serologic markers including anti-HBc (IgM and IgG), HBeAg/anti-HBeAb, anti-HbsAb, quantitative HBV-DNA PCR and liver biochemistry including transaminases, ALP, GGT and bilirubin are considered necessary in order to differentiate between active and inactive liver infection.

Active carrier state is defined as HBsAg(+) in the presence of HBeAg(+) or HBeAb, with HBV viral load above 20000 IU/mL with or without elevated alanine aminotransferase (ALT) levels whereas inactive carriers are HBsAg(+) and negative for HBeAg(-) with persistently low viral load, normal liver enzymes and low anti-HBc IgM or anti-HBc IgG levels[6]. The occult HBV carrier state refers to a rare subgroup of patients who are HBsAg(-), most often with detectable anti-HBc but low viral load without liver enzyme elevation[7].

According to these definitions, the most cost-effective strategy is to screen and monitor all dialysis patients with basic serology which includes HBsAg, anti-HBc and anti-HBs. HBV PCR should be performed in the few cases of isolated anti-HBc positivity in order to detect occult carriers, especially among those on the waiting list[8].

In active HBV carriers on hemodialysis, therapy with one of the available antiviral agents is indicated until HBeAg becomes negative and viral replication is suppressed. Inactive carriers should be monitored with HBV-PCR and liver enzymes.

By interpreting HBV serology and virology in hemodialysis patients, it is essential to take into consideration the altered natural history of hepatitis B in this patient setting. HBV infection is usually asymptomatic even in the acute phase, transaminase levels are lower compared to the general population and seroconversion

from HBeAg to anti-HBeAb or from anti-HBc IgM to IgG is delayed or does not occur, even after resolution of the active infection[9]. About 80% of HBV infected dialysis patients progress silently to a chronic carrier state[10].

While on the waiting list, dialysis patients should be monitored every 6-12 mo with HBV-DNA and transaminase levels. Wait-listed transplant candidates must be either inactive carriers or sustained viral responders (SVR) with persistently low, or undetectable HBV-DNA.

Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend performing a liver biopsy in hemodialysis patients that are candidates for a kidney allograft and are positive for HBsAg, so that hepatitis' severity is assessed. After baseline histological evaluation, candidates should repeat liver biopsy every 3-5 years, if there is ongoing viral replication[11].

Currently, non-invasive tools for the assessment of hepatitis stage are available. The biochemical indices as the APRI score, though useful in the general population, have a reported diagnostic accuracy of about 50% in dialysis patients[12]. The same applies for transient elastography, a routine applied noninvasive tool aiming to assess hepatic fibrosis by liver stiffness measurement (LSM). Unfortunately, both in HBV infected hemodialysis patients and kidney recipients it has not yet been validated. Liver stiffness measurement is influenced by the fluid volume of the patient, which complicates the interpretation of the results due to the discrepancy between pre- and postdialysis values[13]. In a single center cohort of 284 dialysis patients with hepatitis C transient elastography demonstrated high diagnostic accuracy without diminishing the need for further validation, especially in pre-transplant control[14]. Still, in regards to kidney transplant candidates, performing a liver biopsy continues to be considered the "gold standard".

Liver cirrhosis has been regarded for a long time as a definite contraindication for lone kidney transplant with a combination of kidney-liver transplantation being considered the established therapy option. On the other hand nowadays, using new nucleotide analogues often leads to sustained viral response, fibrosis regression and the eventual evolution to a stage of septal inactive cirrhosis. In such cases, a follow up biopsy - 12 mo after the original SVR-must be performed and if the disease remains inactive, the patient may move to the waiting list and possibly undergo lone kidney transplantation[15].

A recent single center study provided data of an excellent five-year survival rate (94%) in 12 cirrhotic patients with hepatitis B after kidney transplantation alone[16].

Routine evaluation for hepatocellular carcinoma (HCC) with liver ultrasound and alfa-fetoprotein values every 6 mo is recommended in all dialysis patients with advanced fibrosis or pre-cirrhotic stage[11].

HBsAg(+) prospective kidney donor

HBV transmission from donor to recipient may occur in kidney transplantation as in all solid organ transplantations. HBV-infected donors' kidneys may be safely used under certain conditions and thus avoid unnecessary organ discarding especially in countries with organ shortage and low HBV prevalence. The routine serologic evaluation of a potential living or deceased donor includes HBsAg, antiHBc and HBsAb. The risk of HBV transmission *via* donation depends on the donor's serologic status.

HBsAg(+)/antiHBc(-)/antiHBs(-): Kidney transplantation is not suggested when the donor is HBsAg(+) and the recipient is HBV naïve since it poses an increased chance of an acquired infection which in most cases has an aggressive progression[17]. Jiang *et al*[18], however, have shown that allografts from HBsAg (+) donors may safely be used in transplantation when the recipient is HBsAg(-) independent of immunity type. This applies to all HbsAg(+) patients with a titer count of more than 10 IU/mL simultaneously receiving hepatitis B hyperimmune globulin (HBIG) independently of whether they are receiving an additional vaccine dose. Even though the probability of transmission is relatively small, it is imperative in such cases to obtain a written informed consent after fully briefing the patient prior to moving along with kidney transplantation. Singh *et al*[19], describe a successful transplantation in 104 anti-HBs(+) patients. Twenty seven recipients received only the original vaccination whereas, the rest concurrently received additional vaccine dose, HBIG and other antiviral medication.

At Laiko hospital in Athens, this kind of renal transplantations from seropositive donors to seronegative or HBs antibody positive patients independent of immunization type (past infection, vaccine) are only allowed when the recipient's titers are at least 10 IU/mL. All recipients receive one booster vaccination dose combined with HBIG just before transplantation. After the introduction of Entecavir such recipients receive post transplantation antiviral prophylaxis for 6 mo. Following this protocol, we have performed 13 transplantations from HBsAg(+) donors to immunized recipients with excellent long term results (unpublished data).

Another safe way to avoid unnecessary organ discarding especially in endemic areas, is to transplant kidneys from HBsAg(+) donors into HBsAg(+) recipients, a practice which offered successful results. In Greece, the allocation policy allows such transplantations, which are also performed in our center with good results.

HBsAg(-)/antiHBc(+)/antiHBs(+): Kidney transplant donors with this serologic profile are considered safe, since there is no way to transmit HBV to the kidney recipient**.** A single case report describes HBV transmission from a multiorgan donor only to the reciepient of the liver graft[20].

HBsAg(-)/antiHBc(+)/antiHBs(-), *i.e.*, isolated

presence of anti-HBc: The risk of HBV transmission from donors with this serological profile, though very low, has not been completely clarified. A recent analysis that examined transplants from anti-HBc(+) donors to 1385 HBsAg(-) recipients found seroconversion to HbsAg-positivity only in four recipients (0.28%) and to anti-HBc-positivity in 32 patients (2.3%)[21]. These donors should preferably be checked for the presence of anti-HBcIgM in order to exclude recent infection. Unfortunately, in relation to deceased donors, such testing is due to time constraints practically impossible. Renal transplantation should however be at the very least considered, since transmission risk is significantly smaller than from HBsAg(+) donors[22,23]. If one selects the safer side, it is preferable to apply the protocol relevant to HBsAg(+) donors.

OUTCOMES OF HBV INFECTED PATIENTS AFTER KIDNEY TRANSPLANTATION

HBV infection is associated with worse survival rates for seropositive patients in comparison to seronegative ones. In a 2005 study with an overall population of 6050 seropositive renal transplant recipients, Fabrizi *et al*[24] calculated a relative death risk of 2.49. The respective graft loss risk was 1.44.

On histological level, the severity of chronic hepatitis B increases during the post-transplantation period and is characterized by higher rates of progression to cirrhosis and mortality due to liver failure. Moreover, HBV(+) renal transplant patients are at increased risk of hepatits B reactivation which may rarely manifest as fulminant hepatitis with massive necrosis or as severe cholestatic hepatitis[25].

The only study of renal transplant patients' liver biopsies did not detect histological worsening in only 15% of seropositive recipients. Following the kidney transplantation, 28% of the patients progressed to liver cirrhosis whereas none had developed it beforehand. Twenty-three percent of the cirrhosis patients also developed hepatocellular cancer[26].

Survival rates for HBV infected kidney transplant recipients have since 1986 significantly increased due to the extensive use of antiviral agents. In a small Italian study, the authors reported that 67% out of the 42 HbsAg(+) patients that received a renal transplant from 1976 to 1982, achieved a survival rate of 12 years[27]. Similarly, Yap *et al*[28], reported that 81% amongst 63 seropositive kidney allograft recipients that received nucleoside/nucleotide analogues therapy, achieved a survival rate of 10 years. Liver failure, however, is still the leading cause of death for this cohort.

ANTIVIRAL TREATMENT IN KIDNEY TRANSPLANTATION

Goal of antiviral treatment

The therapeutic aim is to effectively suppress viral replication, prevent hepatic fibrosis, and at the same time minimize drug resistance. In order to systematically measure the patients' response to therapy, we must measure HBV DNA levels because ALT has a low reliability as a marker of liver disease activity.

Antiviral treatment strategies in kidney transplant recipients: Preemptive administration or prophylaxis?

The introduction of antivirals after transplantation aims to prevent immunosuppression-induced increase of viral replication which may lead to hepatitis B reactivation. The latter is defined by high viral load and or biochemical hepatitis. Virus reactivation is diagnosed by redetection of previously negative HBV-DNA using a highly sensitive assay with a cut off level less than 20 IU/mL, while "hepatitis" diagnosis relies on > 3 fold increase of ALT levels or an absolute increase in ALT above 100 IU/mL. Reverse seroconversion means redetection of HBsAg or anti-HBcAg when previously negative[29].

Antiviral prophylaxis means that treatment is initiated in inactive carriers in order to prevent HBV reactivation. The term "universal prophylaxis" is used when treatment is applied to the entire population at risk as for example to all kidney recipients under treatment with immunosuppression. Preemptive treatment defines antiviral administration after the reappearance of viral load or after the occurrence of seroconversion. According to recent guidelines, universal prophylaxis is recommended for all patients of moderate to high risk for viral reactivation during immunosuppression[30].

Treatment initiation: When should antiviral prophylaxis start?

Antiviral prophylaxis must begin before or at worst immediately after transplantation. A study of 15 patients with normal transaminase levels before transplantation, showed that the 7 that started LAM therapy along with the procedure had undetectable HBV DNA levels for the duration of the observation period. Half of the patients that didn't receive early treatment presented transaminase elevation during the first post-transplantation year[31].

Currently available antiviral agents and their use in kidney transplantation

A number of antivirals agents are available to treat hepatitis B. They include: Pegylated interferon alfa 2a, interferon alfa-2b as well as the nucleoside analogues LAM, telbivudine, tenofovir, entecavir, and adefovir.

Interferon and PEG-INF

The use of interferons following kidney transplant procedure is no longer advised since these agents have led to immunomodulatory effects and ultimately either to graft rejection or to hepatitis reappearance at a rate of almost 80% after suspending treatment[32].

LAM

LAM is a nucleoside reverse transcriptase inhibitor

and has been considered the best therapeutic option and it was the first such agent to be approved for clinical use in HBV infected kidney allograft recipients. The prophylactic use of LAM post-transplantation has offered long-term efficacy. A meta-analysis of 14 clinical trials with a total of 184 recipients that received LAM, indicated in 91% of them untraceable viral cargo and normal liver enzyme in 81%, for a significantly long time[33].

Prolonged treatment with LAM, however, eventually leads to the treatment resistance. In most cases resistance occurs due to a mutation in the tyrosine-methionine-aspartate-aspartate (YMDD) locus of HBV DNA polymerase[34]. The clinical presentation of resistance varies. Some patients show only reappearance of serum HBV DNA while others present with HBV reactivation.

The rate of LAM resistance varies from 20% up to 60% in different studies[35,36]. Following 29 kidney allograft recipients for a mean period of 69 mo, Fabrizi *et al*[34], reported that 48% of them (14/29) developed LAM resistance, whereas all 14 of them had YMDD mutation. Out of these patients that presented resistance, 79% had a disease flare.

Prolonged period of therapy is positively linked with resistance to LAM with the cumulative probability reaching 60% after 69 mo of therapy[33,35]. Patients with LAM resistance should be treated preferably with adefovir or tenofovir, if renal function permits or alternatively with entecavir.

Even though LAM is not nephrotoxic, it is removed by the kidney, and therefore the dose ought to be adjusted to the patient's renal function. The recommended dose for patients with estimated GFR > 50 mL/min per 1.73 m^2 is 100 milligram per day and 100 milligram every second day for those that present kidney injury/failure.

Most importantly, after systematic use of LAM prophylaxis, survival rates in HBV infected kidney transplant recipients have increased progressively with 81% of them reaching a survival rate of ten years, which is very similar to that of seronegative patients[37].

Entecavir

Entecavir is an analog for guanosine and is considered to be much more effective compared to LAM. It has a high antiviral potency, a high genetic barrier for resistance, a good safety profile and is effective in treatment of naïve as well as of LAM treated patients without resistance.

There is significant evidence of its ability to successfully suppress the virus for a prolonged time. Hu *et al*[38] recently, in 2012, studied 18 (67% of total cases) naïve renal transplant recipients and 9 (33%) recipients that had been previously treated with LAM but without resistant mutations, entecavir was successful in clearing HBV DNA in 70%, 74%, 96% and 100% of patients after 12, 24, 52 and 104 wk respectively. Moreover, compared to LAM, entecavir reached at the same time of treatment higher rates of undetectable HBV DNA (32% *vs* 70%, 37% *vs* 74%, 63% *vs* 96% and 63% *vs* 100% of patients at 12, 24, 52 and 104 wk respectively; $P < 0.005$).

LAM resistant HBV patients, however, do not show similar results. Complete response to entecavir may take more than 6 wk and may not be achieved at all. Entecavir use in LAM or adevofir resistant kidney allograft recipients, was studied by Kamar *et al*[39], examining 10 patients with solid organ transplantation, that included eight renal transplant recipients. After 16.5 mo of therapy, there was a variable decrease in HBV DNA viral load with 50% succeeding in clearing HBV reporting no important unwanted reactions.

Between kidney allograft recipients there are no reported Entecavir-resistant cases. Similarly in the general population Entecavir-resistant patients after 5 years of therapy is minimal (1.2%) in naïve patients. On the contrary, in cases with LAM resistance the chance of entecavir-resistant cases increases annually from year 1 to year 5 (6%, 15%, 36%, 46% and 51% respectively)[40]. According to recent guidelines, entecavir has displaced LAM as first line prophylaxis in HBV(+) kidney transplant recipients[30].

Adefovir dipivoxil

Adefovir, an acyclic nucleoside, is an adenosine analog and is used both in a single agent therapy or combined to entecavir in HBV infected patients and LAM-resistant cases[41]. It is mainly used in LAM resistant HBV patients either as monotherapy or as "add on" therapy to LAM[42].

It is, however, potentially nephrotoxic. Research on HIV patients indicates that high daily doses of adefovir (60-120 mg) could result in renal tubular injury[43]. In a study of 11 renal transplant recipients with LAM resistance that were treated solely with adefovir by Fontaine *et al*[44], dosage was adjusted according to renal function. After 12 mo, serum HBV DNA declined satisfactorily and no hepatitis B reactivation was observed. There was no evidence of nephrotoxicity with no significant adverse events and the drug seemed to be well tolerated. In an analogous study of 11 kidney LAM resistant transplant recipients, adefovir was administered at very low doses according to GFR (2.5-10 mg/d) and showed good efficacy in terms of reducing HBV DNA viral load and normalizing liver enzymes after two years of therapy. Renal parameters were closely monitored and showed a slight increase in creatinine (from 125 ± 35 to 141 ± 32 mmol/L, $P = 0.02$), an increase in proteinuria as well as slight impairment of proximal tubular reabsorption[45]. In a series of 14 LAM resistant transplant recipients, adefovir was administered to 5 patients as monotherapy and to 9 as "add on" to LAM. Five out of 14 patients (29%) had a significant decline in GFR (loss of 10 mL/min or more after 32 mo therapy) which led to treatment

discontinuation in 4 of them[46].

Tenofovir disoproxil fumarate

Tenofovir DF as a nucleotide analog reverse-transcriptase inhibitor (NtRTI) selectively inhibits viral reverse transcriptase, a crucial enzyme in retroviruses such as human immunodeficiency virus and hepatitis B virus, while showing limited inhibition of human enzymes, such as DNA polymerases. Tenofovir has a strong antiviral effect, prevents viral replication and is used in the therapy of naïve patients and those that present LAM resistance[47,48]. In a study with HBV infected patients of the general population, this nucleotide analog had a strong effect when used to treat patients with LAM resistance, while no tenofovir-resistant cases appeared during a forty eight month post-therapy follow up[49]. Still, the shortage of data referring to kidney transplant recipients leads to concerns for potential kidney injury. In a pilot study by Daudé *et al*[50], 7 solid organ recipients - 3 with kidney transplantation - received tenofovir as rescue therapy after resistance to other nucleoside analogues. After 12 mo, there was effective suppression of viral replication with HBV clearance in 3 out of 7 patients.

Telbivudine

Telbivudine is ineffective in LAM resistant HBV renal transplant recipients, due to cross-resistance to entecavir and LAM. There is not enough information regarding telbivudine in the area of kidney transplant recipients.

Treatment duration: Is discontinuation of antivirals feasible?

In the general population the duration of antiviral treatment with nucleoside analogues still remains unclear, since nucleoside analogues cannot completely eradicate HBV[51]. The duration of antiviral therapy for renal transplant patients is even more difficult to assess, while data referring to long term outcomes after nucleoside analog withdrawal in immunosuppressed patients including kidney transplant recipients are lacking. The prophylactic or preemptive use of LAM initially and the newer nucleoside analogues later on, have indeed changed the picture in kidney transplantation, with HBV(+) recipients reaching significantly better long term outcome worldwide. Nevertheless, there are still unresolved issues concerning the use of antivirals in transplantation. Solid organ recipients including kidney, are receiving lifelong immunosuppression. Consequently, one logical assumption might be that they also need lifelong prophylaxis to prevent viral breakthrough or reactivation. On the other hand, "lifelong" antiviral prophylaxis, besides cost, is associated with various problems. The main issue is the development of resistance, primarily to LAM but *via* cross-resistance also to the newer agents as entecavir and to a lesser degree adefovir and tenofovir. Rates of LAM resistance increase with increased therapy duration and approach 60% after 5 years of treatment[35]. Therefore, the prophylactic use of entecavir as first line prophylaxis has already been implemented following recent guidelines. Unfortunately, entecavir is much more expensive and has not been widely approved, especially in developing countries. Furthermore, adefovir and tenofovir are both nephrotoxic[43,46] and with the lower doses used as prophylaxis in kidney transplantation, their long term therapeutic efficacy has not yet been proven.

After the development of resistance, combination therapies are indicated either by switching from LAM to entecavir and tenofovir or as "add on" to LAM. Combination therapies have the same adverse effects and are even more expensive than single agents. Last but not least, nucleoside analogues interfere with immunosuppressive agents as calcineurin inhibitors, making patient monitoring after transplantation even more complicated.

For all these reasons, the feasibility of treatment discontinuation remains one of the most important, yet unresolved issues in HBV(+) kidney transplantation. The first attempt for LAM discontinuation was published by Chan *et al*[52] in 2002. LAM was discontinued in 12 low-risk kidney recipients after stabilization. Withdrawal was successful in 5 patients (41.7%)[53]. Another study retrospectively followed a small cohort of of 14 HBsAg(+) renal transplant recipients. In six of them, antiviral therapy seized after a median of 14 mo. Each of them was on stable maintenance of immunosuppression without any sign of viral activity. After discontinuing antiviral treatment and following the patients for a median of 60 mo, 4 of them (67%) presented no sign of viral breakthrough or HBV re-activation. In the last 2 cases who presented HBV reactivation, antiviral treatment was subsequently reinstated leading to HBV clearance[54]. Despite the small number of cases in both studies, they provide promising results for further investigation.

To sum it up, post renal transplantation antiviral therapy could be withdrawn in cautiously chosen subsets of patients that fulfil certain criteria: Stable renal function, low immunological rejection risk, a minimum of 6-9 mo low-dose maintenance immunosuppression, no evidence for HBV activity and a minimum of 12 mo therapy with antiviral agent without developing resistance. Frequent measurement of HBV-DNA levels and 3-6 mo testing of liver enzymes are essential while antiviral treatment ought to be reinstated if immunosuppression grows, *i.e.,* in the case of antirejection therapy.

IMMUNOSUPPRESSION IN THE COURSE OF HBV AFTER KIDNEY TRANSPLANTATION

There is an association between immunosuppression and HBV reappearance, both in seropositive patients,

and in those positive for anti-HBc/anti-HBs, most frequently in a titer count that is quite low, *i.e.,* previously infected patient[55]. Most data derive from HBV infected patients that receive treatment for either solid organ or hematological malignancies[55,56].

Recipient's immunocompetence as well as the overall level of immunosuppression are highly associated with HBV reactivation after transplantation. Immunosuppression affects the relationship between the host and HBV possibly resulting in serious liver damage. Immunosuppressionmay lead to liver injury through two distinct routes. One pathogenetic pathway is virus hepatotoxicity due to unrestrained intracellular viral replication resuting from diminished host immunosurveillance. Such a risk is intimately associated with the initial phase, during which the overall burden of immunosuppression is elevated while the most severe clinical manifestations are fibrosing cholestatic hepatitis (FCH) and fulminant liver failure. FCH has been initially described as complication of HBV infection in liver grafts. A small number of FCH cases with dismal course have been reported in renal transplant recipients as well without differing histologically from FCH manifesting in liver allografts[57-59].

The second pathway involves secondary immune mediated liver injury occuring when immunosuppressants are withdrawn and immune efficiency is reconstituted. The host immune response destroys HBV infected hepatocytes leading to extensive parenchymal necrosis. This pathway has mainly been observed in solid organ and hematologic malignancies cases even after 6 to 12 mo having completed chemotherapy. In renal transplantation, this process may lead to accelerated liver damage after rapid reduction of immunosuppression, usually after tapering of the high corticosteroid-doses given for anti-rejection therapy[56].

Immunosuppressants

The traditional immunosuppressive agents that may be prescribed in different permutations for renal transplant recipients are: Corticosteroids, azathioprine, mycophenolate acid derivates (MMF/MPA), calcineurin inhibitors (cyclosporin, tacrolimus), and the well known inhibitors of mammalian target of rapamycin (mTORi's: Everolimus, sirolimus). There are two more groups of immunosuppressants; Monoclonal antibodies (anti-CD20 Rituximab, anti-IL2 Basiliximab) and polyclonal antibodies as ATG (antithymocyte globulin) that may be prescribed for either induction or rejection therapy.

According to the KDIGO guidelines all immunosuppressive agents currently used for induction and maintenance immunosuppression in kidney transplantation can be used in HBV(+) recipients[11]. They all increase replication of the virus and may lead to increased chances of HBV reactivation. The American Gastroenterological Association (AGA) has assessed the HBV reactivation risk depending on the use of particular immunosuppressants[30].

Rituximab

Rituximab is considered to have the most elevated risk for HBV reactivation (> 10%) from all immunosuppressive agents that are used in renal transplantation, according to AGA guidelines[30]. Furthermore, this risk may continue up to 12 mo, due to the prolonged duration of the antibody's immune reconstitution. Rituximab is linked to HBV reactivation in HBsAg(+) but also in recipients with anti-HBc possitive and those with anti-HBs positive (reverse seroconversion). In a retrospective analysis, 24.3% between 230 B-cell lymphoma patients, HBsAg-negative patients that received rituximab, were anti-HBc(+). Reactivation oft he virus was observed in 8.9% of patients. Entecavir use led to HBV DNA clearance and allowed for the re-administration of rituximab[60].

Polyclonal antibodies (Antithymocyte globulin)

After administering antithymocyte globulin to patients with severe aplastic anemia, increased rates of viral replication have been reported in HSV, EBV and CMV infections. More specifically, in those cases ATG was given concomitantly with cyclosporin[61]. There is a shortage of reliable data in relation to HBV reactivation after ATG therapy.

Corticosteroids

Corticosteroids (CS) are the most commonly used immunosuppressant in the world. They are, however, undeniably related to elevated viral replication. HBV reactivation risk is dependent upon the dose as well as on the duration of CS use. High CS doses increase viral load even though ALT may decrease. During steroid tapering, one finds the opposite effect with influenced liver enzymes four to six weeks following withdrawal[56,62]. As stated by American Gastroenterological Association, doses of prednisone of 20 mg per day or/and long periods of administration (> 3 mo) could increase the risk for reactivation of hepatitis B along with quick reduction, because of immune modification[30].

In relation to renal trnsplantation, increased doses of corticosteroids are used in the first wk post transplantation; the doses are reduced from that point on and for the next 3-6 mo, eventually leading to a prednisone standard of 5 mg every day or second day. Corticosteroids can totally be sidestepped (steroid-avoidance regimens) or at least could be retracted at four to six weeks or more (steroid-sparing regimens), in stable and low immunological risk cases with outstanding outcomes. In HBV renal transplant patients, CS should be administered at the lowest possible doses and ideally should be withdrawn or even totally abandoned in low immunological risk cases.

Calcineurin inhibitors

Tacrolimus and ciclosporine continue to be the mainstays of immunosuppressive regimens in renal transplant

recipients. There is enough evidence that cyclosporin leads to *in vitro* reduction of viral replication[63,64]. Today, most immunosuppressive treatments are based on tacrolimus. Despite the lack of definitive guidelines, many people support the use of cyclosporin instead of tacrolimus in HBV infected renal transplant patients. Some others prefer to withdraw steroids from a tacrolimus-based regimen. Due to the lack of definite guidelines, choosing between the two calcineurin inhibitors depends on each hospital's practice.

Antimetabolites

Even though, azathioprine is considered to be hepatotoxic, it has not been linked when administered as monotherapy to elevated HBV reactivation risk. Still, the use of more potent and more selective antimetabolites as MPA's, has limited azathioprine use in renal transplantation to patients with special indications[65].

Mycophenolate acid derivates

Azathioprine has been replaced by mycophenolate mofetil and its most recent derivate mycophenolate sodium in the majority of immunosuppressive treatments. There is no definite data about MPA's and HBV reactivation. They are, however, generally considered to be safe for HBV renal transplant patients.

Mamalian target of Rapamycin inhibitors

The reactivation of HBV under treatment with mamalian target of Rapamycin (mTOR) inhibitors has not been examined in kidney transplantation but normally their safety is not disputed. Everolimus when used as a chemotherapeutic agent has been reported to lead to HBV reactivation. The doses, in those cases, however were more elevated compared to accustomed ones prescribed as standard immunosuppressive regimen in renal transplant recipients[66].

Summarizing, all immunosuppressive agents used in renal transplantation could be administered in HBV positive patients. There is no evidence for any specific effect of a particular immunosuppressive agent on viral replication since it is associated with the total amount of immunosuppression. Efforts to minimize immunosuppression-induced viral reactivation should focus on minimization of the total immunosupression burden long term, which is more important than the choice of one single agent over another. Minimization protocols, especially corticosteroid-avoiding or sparing protocols, are preferable and should be applied to low-immunological risk HBV(+) recipients. Close HBV monitoring is mandatory whenever the total immunosuppression status is altered.

CONCLUSION

In the era of potent antivirals and with evolving knowledge and mounting evidence in the areas of both kidney transplantation and hepatitis B, HBsAg(+) renal transplant candidates and recipients can be monitored and successfully treated, reaching survival rates that are comparable to their HBsAg(-) counterparts. Furthermore, under certain conditions kidneys from HBsAg(+) donors can be safely transplanted into immunized recipients thus avoiding unnecessary organ discard.

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