Occult Hepatitis B Infection in Kidney Transplant Patients

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ABSTRACT

Occult hepatitis B infection (OBI) is still a topic of debate worldwide. It is defined as the presence of hepatitis B virus (HBV) DNA in serum and/or liver from HBsAg-negative subjects. OBI may lead to the development of cirrhosis and hepatocellular carcinoma. It continues to present several unique challenges in organ transplantation despite the availability of an effective vaccine to prevent HBV infection and the introduction of oral therapy to treat HBV infection. HBV reactivation following organ transplantation can occur even in recipients with absent hepatitis B surface antigen and remains an important cause of morbidity and mortality. Concerning OBI complications, the screening of HBV DNA by the highly sensitive molecular means should be implemented for both recipients of organ transplant and organ transplant donors especially in highly endemic areas of HBV. In the era of potent antivirals and with evolving knowledge, HBsAg (+) renal transplant candidates and recipients can be monitored and successfully treated. Kidney organs from HBsAg-negative and anti-HBc–positive donors should be considered for transplant candidates after weighing the risk-benefit ratio. All transplant candidates should receive HBV vaccination if they are not immune to facilitate receipt of an organ from a donor with anti-HBc seropositivity.

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ABSTRAK

Infeksi hepatitis B tersamar masih menjadi topik perdebatan di seluruh dunia. Hal ini didefinisikan sebagai adanya DNA virus hepatitis B (HBV) dalam serum dan/atau hati dari subyek HBsAg-negatif. OBI dapat menyebabkan perkembangan sirosis dan karsinoma hepatoseluler. Hal tersebut dapat menimbulkan komplikasi organ transplantasi organ meskipun tersedianya vaksin yang efektif untuk mencegah infeksi HBV dan pengenalan terapi oral untuk mengobati infeksi HBV. Reaktivasi HBV setelah transplantasi organ dapat terjadi bahkan pada penerima yang tidak memiliki antigen permukaan pada hepatitis B dan tetap menjadi penyebab penting morbiditas dan mortalitas. Berkenaan dengan adanya komplikasi, skrining DNA HBV dengan cara molekuler yang sangat sensitif harus dilaksanakan baik untuk penerima transplantasi organ dan donor transplantasi organ terutama di daerah yang sangat endemic HBV. Di era antivirus yang kuat dan dengan pengetahuan yang berkembang, kandidat dan penerima transplantasi ginjal HBsAg (+) dapat dipantau dan berhasil diobati. Organ ginjal dari donor HBsAg-negatif dan anti-HBc-positif harus dipertimbangkan untuk...
INTRODUCTION

Hepatitis B virus (HBV) infection is still a major public health problem worldwide with more than two billion people being infected with HBV and more than 360 million people suffering from chronic HBV and becoming carriers.\(^1\) Two-thirds of HBV carriers live in Southeast Asia and Indonesia has moderate to high HBV endemicity.\(^1\)

HBV can cause acute, chronic, and sometimes occult infections. HBV infection is generally diagnosed when circulating hepatitis B virus surface antigen (HBsAg) is detected in the serum. If the hepatitis B virus genome (HBV DNA) is detected in an HBsAg negative individual, the condition is referred to as occult hepatitis B infection (OBI).\(^3\) The existence of OBI has been suggested since the early 1980s but has only been well identified in the last 10 years after the discovery of highly sensitive molecular biology techniques.\(^4\) But, OBI is still a topic of debate around the world.

Occult hepatitis B infection (OBI) brings several health problems. First, the prevalence is quite high, even a study showed OBI in 18% of those with serological evidence of previous HBV infection and in 8% of HBV seronegative individuals. Second, the persistence of OBI can lead to cirrhosis and hepatocellular carcinoma, similar to non-OBI. Third, it can be transmitted through blood, including in patients undergoing hemodialysis. Fourth, it is often found in the immunocompromised such as kidney transplant donor.\(^2,5\)

Kidney transplantation is the first-choice treatment for end-stage renal disease (ESRD).\(^6\) In transplant recipients, immunosuppressant drugs are used to improve the acceptance of the transplanted organ. In contrary, this immunosuppressant increase risk of HBV infection and reactivation includes OBI spectrum.\(^2,5,6\) Data shows HBV infection occurs in 2.2–20.9% of kidney transplant recipients and 2% of undetected DNA before transplant become OBI 3 months after transplantation.\(^3\) In addition, OBI in renal transplant increased overall mortality, graft damage, and development of liver disease.\(^7\) So that, screening for HBV in this population is recommended by international guidelines.\(^6,8\) But even that, comprehensive review about OBI in renal transplant is limited. So that, this overview is address to in depth review of OBI especially in renal transplant.

DEFINITION AND DIAGNOSIS OF OCCULT HEPATITIS B INFECTION

Occult hepatitis B infection (OBI) is an asymptomatic and difficult-to-diagnose hepatitis B virus infection. There are several definitions of OBI that have been proposed by many experts. Bremer et al emphasized that the term "occult hepatitis B" described the presence of replication-competent HBV DNA (i.e., episomal HBV covalently closed circular DNA [cccDNA]) in the liver in the absence of detectable HBsAg in the serum.\(^4,9\) This often happens after progressive disappearance of serum HBsAg after several years of infection and persists in low-level carriers (HBV carriers with very low levels of viremia).\(^10\) The initial phase of HBV infection before HBsAg appears is not considered OBI because the infection eventually becomes apparent.\(^10,11\)

A more specific definition was proposed by Allain who described OBI as the presence of HBV DNA in the absence of HBsAg, with or without the presence of anti-HBc or anti-HBs outside the acute phase period.\(^12\) Gerlich et al conducted a study by identifying two blood donors who had HBsAg and negative HBV DNA but were transmitting HBV.\(^13\) Later in both cases, the disease progressed as indicated by the detection of HBsAg and the incidence of acute hepatitis. Such cases, according to some literature, are classified as transient OBI which is quite rare and should not be considered as true OBI. This condition may be associated with the presence of HBV immune complexes and/or HBsAg with anti-HBs. True OBI cases showed negative HBsAg during the entire phase. The development of HBV markers during the early phase of true OBI is still not well understood. Even though a transient strong HBV replication occurs, serum HBsAg is detected significantly less than usual.

The European Association for the Study of the Liver (EASL), defines OBI as a condition characterized by the detection of HBV DNA in the liver through a
biopsy procedure; serum negative HBsAg; positive antibodies to HBeAg (anti-HBc); either seropositive or seronegative anti-HBs; and recommends a threshold value for serum HBV-DNA (<200 IU/mL). Although detection of HBV DNA in the liver is the most accurate way to identify OBI, its use is limited in clinical practice because invasive procedures possess risks. Assays of viral genomes in peripheral blood mononuclear cells (PBMCs) have been suggested to reveal occult infections that are not detectable by serological methods or assays for viruses in serum.

Epidemiology

Approximately 240 million people become chronic carriers of HBsAg, with regional variations in the level of endemicity between low (<2%) and high (>8%). This related to increasing of deaths related to HBV infection due to liver cirrhosis and/or hepatocellular carcinoma (HCC), increased by 33% between 1990 and 2013, with the number of cases reaching 686,000 in 2013 worldwide.

Estimating the epidemiology of OBI is difficult because it depends on the capability of the examination tools and the availability of different supporting examinations in each place. Higher HBsAg sensitivity reduces OBI prevalence while increased HBV DNA detection increases OBI prevalence. The prevalence of OBI in the general population depends on the level of endemicity of HBV infection in an area. In areas with high HBV endemicity (East Asia and West Africa), the prevalence of OBI is estimated at 1:100-1,000. In areas with low endemicity (Western Europe, North America, and Australasia), the prevalence of OBI is estimated at 1:5,000. An Italian OBI prevalence study compiled 98 general population liver specimens from liver disease-free and HBsAg-negative individuals. The researchers detected HBV-DNA in 16 samples (16.3%); with positive anti-HBc in 10/16 samples (62.5%). The percentage of OBI from all cases of HBV infection was relatively small, ranging from 0.1% to 0.6%. Many studies only used anti-HBc as the serologic marker for HBV infection, thus caused a bias regarding the true epidemiology because most cases can also occur in anti-HBs positive individuals. The prevalence of OBI was higher in men than women. The prevalence also varied according to genotype, with genotypes D and E as the most common ones. OBI was more frequently identified in the ≥ 50 years age group. The prevalence of OBI was high among chronic liver disease (CLD) patients, the percentage ranges between 40% and 75% in HBsAg negative hepatocellular carcinoma (HCC).

Along with the increased sensitivity of HBV DNA detection methods, more cases of OBI will be identified. However, the clinical significance of this very low viral genome level has to be determined. Accurate unbiased epidemiological studies should be carried out in the general population, especially in areas with a high prevalence of infection. HBV infection occurs in 2.2-20.9% of kidney transplant recipients and is associated with increased overall mortality, graft damage, and progression of liver disease following kidney transplantation.

In general, the immune status of the recipient is strongly associated with the reactivation of HBV after transplantation. Immunocompromised conditions in patients with chronic kidney disease combined with immunosuppressive therapy affect the relationship between the host and HBV which may result in more serious liver damage.

Pathogenesis

Liver injury due to HBV infection in kidney transplantation can occur through two different mechanisms, immunocompromise and autoimmune. The immunocompromise mechanism occurs through uncontrolled intracellular viral replication due to weakened host immunosurveillance. In general, HBV is non-cytopathic, but HBV is thought to be able to directly injure hepatocytes under special conditions which cause uncontrolled viral proliferation, resulting in overproduction of viral particles and antigens. Various studies have shown high rates of viral replication and antigen expression, reinforcing the idea that HBV can be cytopathic under certain circumstances. Such risk is closely associated with an increased immunosuppressive burden with the most severe clinical manifestations being fibrosing cholestatic hepatitis (FCH) and fulminant liver failure. FCH has been reported as a complication of HBV infection in solid organ transplantations. A small number of FCH cases with poor disease course have been reported in kidney transplant recipients.

The autoimmune mechanism is mediated by secondary immunity. This occurs when the immunocompromised condition disappears, and the efficiency of the immune system increases. The host immune response destroys HBV-infected hepatocytes leading to extensive parenchymal necrosis. This mechanism has mainly been observed in solid organs.
and hematological malignancies even after 6 to 12 months after completion of chemotherapy. In kidney transplantation, this process can lead to accelerated liver damage after a rapid decrease in immunosuppression levels, usually after a reduction of corticosteroid dose for anti-rejection therapy. OBI was associated with poorer survival rates especially in seropositive patients compared to seronegative patients. A study involving 6,050 seropositive kidney transplant recipients found a relative risk of death of 2.49 and the respective risk of graft loss was 1.44 with 95% CI: 1.02–2.04. Histologically, the severity of chronic hepatitis B increases during the post-transplantation period and was characterized by a higher progression rate to cirrhosis and death from liver failure. In addition, HBV (+) kidney transplant patients are at increased risk of reactivation which may manifest as fulminant hepatitis with massive necrosis or as severe cholestatic hepatitis. After receiving kidney transplants from HBV-infected donors, 28% of patients developed liver cirrhosis. Twenty-three percent of cirrhotic patients also develop hepatocellular cancer. The survival rate for HBV-infected kidney transplant recipients has increased significantly since 1986 due to the widespread use of antivirals. In a small Italian study, the authors reported that 67% of 42 HBsAg (+) patients who received kidney transplants between 1976 and 1982 achieved a 12-year survival rate.

De novo HBV infection has been observed in anti-HBc positive kidney transplant recipients. In a study consisting of 322 OBI patients (negative HBsAg and positive anti-HBc), 4.7% of recipients had de novo HBV infection. HBV reactivation also impacted recipient survival, with patient survival rates at years 1, 3, 5, and 10 being 87%, 79%, 72%, and 65%, respectively, compared with 96%, 94%, 91.5%, and 84.5% in patients without HBV reactivation. Positive anti-HBs with positive anti-HBc did not completely protect against HBV reactivation, as 13.3% experienced HBV reactivation compared with 42% in the positive anti-HBc/negative anti-HBs group. Patients over 60 years of age receiving anti-T-cell antibody immunosuppressive agents were associated with an increased risk of HBV reactivation (11.69 and 4.87, respectively).

Immunocompromised condition in kidney donor recipients is increased due to the administration of immunosuppressants as anti-rejection therapy. The immunosuppressants frequently given to kidney transplant recipients are corticosteroids, azathioprine, mycophenolic acid derivatives (MMF/MPA), calcineurin blockers (cyclosporin, tacrolimus), and mammalian target blockers of rapamycin (mTOR: everolimus, sirolimus). There are also two other groups of immunosuppressants: monoclonal antibodies (anti-CD20 Rituximab, anti-IL2 Basiliximab) and polyclonal antibodies (anti-thymocyte globulin; ATG) that can be

![Figure 1. Pathogenesis of OBI in renal transplant](image_url)
used as therapy. According to the KDIGO guideline, all immunosuppressive agents currently used for the induction and treatment of immunosuppression in transplantation can be used in HBV (+) recipients. However, these agents can increase viral replication and HBV reactivation. Various prevention strategies can be carried out by administering vaccines, HBIG, and antivirals to recipients who will receive transplants from HBsAg positive donors.

DONOR-RECIPIENT COMPATIBILITY

Transmission of HBV from donor to recipient can occur in kidney transplantation just like in all solid organ transplantations. HBV-infected donor kidneys can be used safely under certain conditions. Routine serological evaluation of living or deceased donor and potential donors includes HBsAg, anti-HBc, and HBsAb examinations. The risk of HBV transmission through kidney transplantation depends on the serological status of the donor and the recipients which will be delivered base on table 1 bellow.

Organs from HBsAg-negative and anti-HBc-positive donors may be considered for transplant candidates after detailed discussions with the recipients regarding the risk-benefit ratio. The risk of HBV transmission from anti-HBc-positive and HBsAg-negative donors was highest in liver transplantations, moderate in kidney transplantations, and lowest in thoracic organ transplantations. Ridruejo recommended that the therapy and management of kidney transplant candidates are selected according to HBsAg positivity and liver fibrosis occurrence assessments. Patients with decompensated liver disease and end-stage renal disease must be evaluated for dual liver and kidney transplantation.

Table 1. Recommendation of transplantation base on donor and recipient serological status

<table>
<thead>
<tr>
<th>Donor</th>
<th>Recipient</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg (+), anti-HBc (-), anti-HBs (-)</td>
<td>HBV naive</td>
<td>Not recommended</td>
</tr>
<tr>
<td>HBsAg (+), anti-HBc (-), anti-HBs (-)</td>
<td>HBV negative</td>
<td>May safe (need further consideration)</td>
</tr>
<tr>
<td>HBsAg (-)/anti-HBc (+)/anti-HBs (+)</td>
<td>HBV naive</td>
<td>Not recommended</td>
</tr>
<tr>
<td>HBsAg (-)/anti-HBc (+)/anti-HBs (+)</td>
<td>All serological profile</td>
<td>Safe</td>
</tr>
<tr>
<td>HBsAg (-)/anti-HBc (+)/anti-HBs (-)</td>
<td>Recommended (with low risk transmission)</td>
<td></td>
</tr>
</tbody>
</table>

Tuncer et al found that the use of HBsAg positive HBV DNA negative organ donors in 35 recipients with anti-HBs titers > 10 mIU/mL was proved safe. The KDIGO guideline recommended that recipients with anti-HBs titers < 10 mIU/mL be vaccinated to increase their titers to > 10 mIU/mL. None of the recipients had de novo HBV infections or complications caused by HBV during the 2 years of the research. Another study highlighted the importance of having an anti-HBs titer > 100 mIU/mL in HBsAg-negative recipients regardless of the donor’s HBsAg status.

Transplanting HBsAg-positive grafts to HBsAg-negative patients without adequate prophylaxis carries a significant risk of de novo infection. Before the use of antiviral prophylaxis, the rate of HBV reactivation ranged from 50-94%. Since the effective use of antivirals, the outcome of kidney transplantation in chronic HBV patients has improved significantly. The reported incidence of HBV replication after kidney transplantation now varies from 0% to 6.5%. Despite the protection from HBV vaccination or previous exposure to HBV infection, many hospitals remain reluctant to use HBsAg-positive grafts.

MANAGEMENT

The intensity of the immunosuppressive regimen (especially corticosteroids), antiviral administration, previous immunization against HBV infection, and pre-transplantation anti-HBs titer have been suggested to influence the rate of HBV transmission from anti-HBc-positive grafts. In patients with positive HBsAg and HBV DNA < 2000 IU/mL, preemptive therapy is recommended. In patients with HBV DNA > 2000 IU/mL, curative therapy is indicated. Curative treatment is performed with the administration of HBV antiviral

Table 2. Recommendations for safe anti-HBs titers in organ donor recipients

<table>
<thead>
<tr>
<th>Recommended Anti-HBs recipient titer target</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 mIU/mL</td>
<td>Vaccination</td>
</tr>
<tr>
<td>&gt; 10 mIU/mL</td>
<td>Vaccination</td>
</tr>
<tr>
<td>&lt; 100 mIU/mL</td>
<td>Prophylaxis with hepatitis B immunoglobulins (HBIG)</td>
</tr>
<tr>
<td>&gt; 100 mIU/mL</td>
<td></td>
</tr>
<tr>
<td>Any titer (vaccinated or not, there is no difference in seroconversion risk)</td>
<td></td>
</tr>
</tbody>
</table>

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agents, especially those that have a high genetic barrier against resistance.\textsuperscript{16} In patients with positive HBsAg and undetectable HBV DNA, preventive/prophylactic therapy is recommended. There are many strategies suggested to prevent the increased incidence of post-transplant OBI, from vaccine administration to the use of HBIG and oral antiviral therapy.\textsuperscript{16}

For recipients before kidney transplantation, immunization through HBV vaccination or HBIG administration to achieve anti-HBs titer > 10 IU/L has been shown to protect recipients from anti-HBc positive donors.\textsuperscript{8} It is not known whether higher anti-HBs titers can confer further protection. However, a previous study reported that the anti-HBs titer > 100 IU/L reduced the risk of anti-HBc seroconversion to 4\% compared to 10\% in the anti-HBs titer < 100 IU/L.\textsuperscript{20,24}

Before kidney transplantation, HBV vaccination is recommended for all non-immune (anti-HBs negative) transplantation candidates. If possible, the series of vaccines should be administered before transplantation to non-immune individuals because those are less effective after transplantation. If this is not possible, HBV vaccination is recommended after transplantation for all non-immune transplant recipients. In pre-transplant and immunocompromised conditions, a higher dose vaccine (40 g antigen per dose, compared to the standard dose of 20 g antigen per dose) is recommended because the immune response may be lower than that of the general population. HBV vaccination consists of three doses at 0, 1, and 6 months. Serological testing of anti-HBs should be carried out 1-2 months after the completion of the vaccine series to confirm immunity or the possible need to repeat vaccination and give a booster dose if the titer is decreased.\textsuperscript{24,29}

Antiviral therapy has increased the survival of HBsAg-positive kidney transplant recipients. Previously, recipients with positive HBsAg had a 2.49 times higher risk of death after kidney transplantation. Suppression of HBV titer with nucleos(t)ide analogue (NA) therapy has been shown to lead to a significant increase in survival.

Antivirus should be administered as early as possible in transplant candidates who meet the standard population criteria for HBV therapy and continued post-transplant for varying lengths of time. The antiviral of choice, entecavir is preferred over tenofovir disoproxil given the risk of tubular toxicity. In a recent study in liver transplant recipients, tenofovir alafenamide has shown a better renal safety profile than disoproxil. Further research on the safety and efficacy of these drugs in kidney transplant patients is needed. According to several studies, the overall risk of HBV transmission from HBeAb-positive kidney donors is very low. Despite the low transmission rates, guidelines recommended that HBeAb-positive non-immune graft recipients should continue to receive antiviral prophylaxis.\textsuperscript{29,30}

The optimal duration and timing of antiviral therapy for kidney transplant patients are difficult to assess because data regarding long-term outcomes after administration of nucleoside analogue therapy in immunosuppressed patients including kidney transplant recipients are lacking. However, expert opinions suggested that 6-12 months may be sufficient. It is recommended that antiviral therapy after kidney transplantation be discontinued in a carefully selected group of patients who meet certain criteria including stable renal function, low risk of immunological rejection, minimum 6-9 months of immunosuppression maintenance dose, no evidence of HBV activity, and at least 12 months of therapy with antiviral agents without resistance. Periodic measurement of HBV DNA levels and liver enzyme testing for 3-6 months is very important when performing the antiviral treatment in case of growth immunosuppression, i.e. in patients receiving anti-rejection drug therapy.\textsuperscript{29,30}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Recommended algorithm for the use of prophylactic antiviral therapy in chronic HBV-free recipients receiving non-liver grafts from anti-HBe-positive donors.\textsuperscript{29}}
\end{figure}

Although there are insufficient data to recommend prophylaxis in HBeAb-positive/HBsAg-negative recipients, trials of limited antiviral therapy may be considered especially during the first post-transplant year when immunosuppressive therapy is usually maximal. Alternatively, such patients should be monitored for reactivation (HBV serology/HBV DNA and liver function enzymes) every 3-6 months for at least the first post-transplant year. The use of HBsAg-positive donors in kidney transplantation...
has been reported in several studies. A retrospective longitudinal study in Thailand compared outcomes of renal recipients with anti-HBs titers above 100 mIU/mL who received either HBsAg-positive (with minimal or no viral replication) or HBsAg-negative grafts. Regardless of the donor’s HBsAg status, there was no significant difference in graft and patient survival during a median follow-up of 58.2 months. Another study highlighted the importance of having an anti-HB titer of more than 10 mIU/mL and negative donor HBV DNA to safely use HBsAg-positive grafts. Despite these findings, similar to liver transplantation, many transplant centers are reluctant to use HBsAg-positive grafts for kidney transplantation.29,30

**CONCLUSION**

OBI is HBV infection characterized by the presence of HBV DNA without HBsAg, with or without presence of anti-HBc or anti-HBs. OBI is at risk for kidney transplant donors due to immunocompromised conditions. Although asymptomatic, this condition can also cause liver injury which then progresses to cirrhosis and hepatocellular carcinoma. The mechanism of injury can occur due to immunocompromised or autoimmune mechanisms. Before transplantation, it is necessary to check the availability of donors and recipients serologically. Prophylaxis can be given to recipients who have HBV infection with Lamivudine, Etacavir, Tenofovir or Adefovir.

**REFERENCES**


**Table 3. Choice of antivirus in HBV infection undergoing kidney transplant**

<table>
<thead>
<tr>
<th>Nucleos(t)ide analogues</th>
<th>Oral daily dose for HBV infection</th>
<th>Description/side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine*</td>
<td>Age &gt;18: 100 mg</td>
<td>Non-nephrotoxic. Side effects: gastrointestinal, headache, lactic acidosis. High resistance rate.</td>
</tr>
<tr>
<td></td>
<td>Age 2–18: 3 mg/kg (maximum 100 mg)</td>
<td></td>
</tr>
<tr>
<td>Entecavir</td>
<td>Age &gt; 16: treatment in Nucleoside-treatment-naïve patients (first treatment): 0.5 mg</td>
<td>More effective than lamivudine. Side effects: gastrointestinal, headache, myalgia, neuropathy, lactic acidosis.</td>
</tr>
<tr>
<td></td>
<td>In patients on lamivudine refractory therapy: 1 mg</td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Age &gt;12: 300 mg</td>
<td>Side effects: gastrointestinal, skin rash, lactic acidosis, renal impairment (acute renal failure, acute interstitial nephritis, Fanconi syndrome), decreased bone mineral density</td>
</tr>
<tr>
<td></td>
<td>Ages 2–11: 8 mg/kg (maximum 300 mg)</td>
<td></td>
</tr>
<tr>
<td>Adeovir</td>
<td>In patients on lamivudine refractory therapy: 10 mg</td>
<td>Avoid in patients with serum creatinine more than 150 μmol/L or creatinine clearance less than 40 mL/min</td>
</tr>
<tr>
<td>Tenofovir Alfanamid</td>
<td>25 mg</td>
<td>Limited data used in renal transplantation. Used in liver transplant look promising</td>
</tr>
</tbody>
</table>

*The dose is adjusted according to the eGFR allograft
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