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Editorial

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Dilemma of recurrence of hepatitis B infection after liver transplantation

Despite the dramatic decrease in prevalence of hepatitis B virus (HBV) infection and improvement in the treatment outcomes, the infection still remains a major cause of liver transplantation in the world (1,2). In the past, because of the high rate of HBV recurrence and lower survival of HBV-infected patients, transplantation was contraindicated (3). Immunoprophylaxis with hepatitis B immunoglobulin (HBIG) and oral anti-HBV therapy have improved the outcome of HBV transplanted patients (4). Before using HBIG and oral antiviral drugs, the recurrence of HBV infection after transplantation often led to liver failure and in some cases death. However, there is debate regarding the cost benefit of intervention caused by the recurrence of HBV infection after transplantation. To resolve this issue, more data should be gathered.

In this issue, the study by Xu *et al.* (5) showed that the pre-transplant HBV DNA level and choice of antiviral therapy were identified as major risk factors associated with HBV recurrence after LTx. Does pre-liver transplant HBV DNA level affect HBV recurrence or survival in transplant recipients receiving nucleos(t)ide analogues? The response is positive, but it was better to send the patients for transplantation before occurrence of resistance to antiviral therapy (6). Pre-transplant HBV viraemia especially when it is because of YMDD motif mutations is associated with increased probability of post-transplant HBV recurrence (6). In the Xu *et al.* study about half of the patients did not receive any antiviral therapy before LTx. Furthermore, Xu *et al.* (5) did not find any relationship with recurrence rate of HBV and pre-transplant viral mutations. This issue can be discussed from two sides: on one side, it may be related to a bias in patient selection for antiviral therapy such that those with very low titre or undetectable HBV DNA did not receive any antiviral therapy. On the other hand, it may mean that they sent the cases for LTx before an urgent need for nucleos(t)ide analogues. However, it cannot be concluded that pre-transplant viral mutations cannot increase the HBV recurrence after LTx. Actually because of the deleterious impact of lamivudine resistance on likelihood of HBV recurrence after LTx, today lamivudine monotherapy is not considered as the optimal first-line therapy for patients with HBV-decompensated cirrhosis before LTx (4). Another type of nucleos(t)ide analogue, adefovir monotherapy, is not suitable for such patients because of lower potency in the first year of therapy as well as the risk of resistance to this medication which will be higher after 3 years of consumption (7). Before introduction of new medications such as entecavir and tenofovir most guidelines recommended to use a combination of lamivudine and adefovir (8). Entecavir is a potent antiviral therapy against HBV and is superior to the previous two medications in rendering undetectable HBV DNA level and shows much lower viral resistance rates. Thus, it is one of the first-line therapies in patients with HBV-decompensated cirrhosis before LTx (9). The other potential first-line therapy in this situation is tenofovir. Fortunately, there is no report of any viral resistance to this drug after 96 weeks of treatment (10). We need more trials with tenofovir to make firm recommendations in cirrhotic patients before LTx.

This study by Xu *et al.* (5) showed that the recurrence rate in the first year was much lower than the third year; current guidelines suggest to use a combination of HBIG and nucleos(t)ide analogues after LTx (11). In one study, the overall 1-, 2-, 5- and 10-year HBV recurrence rate was 1.4, 5.5, 7.3 and 8.5 respectively (11). All the transplant recipients had received HBIG combination with nucleos(t)ide analogues after operation and this seems to be the main cause of good survival in the study group (11). Late HBV recurrence is usually caused by the emergence of resistant mutations (12); thus new drugs such as tenofovir may control the recurrence in this situation. However, by increasing the survival of patients after LTx and use of HBIG and nucleos(t)ide analogues, we will start seeing more cases with resistance to these drugs and HBV surface escape mutations in future.

In this study (5), approximately 43% of enrolled cases were hepatocellular carcinoma (HCC) patients. The authors found that presence of HCC and post-transplant viral mutations were the major risk factors associated with HBV recurrence after LTx. Previous studies (13,14) indicated that the recurrence of HCC following LTx is related to HBV recurrence and also may be related to viral mutation. Therefore, we need to consider alternative strategies for control of HBV infection in patients with viral mutation after LTx.

Although HBIG is associated with lower recurrence rate in the LTx setting, the main problem is its high cost. It is an important issue in Asia where HBV is the main indication for LTx. The initial HBIG protocol uses fixed monthly dosages of HBIG as 10 000 IU, aiming to maintain anti-HBs titles more than 500 IU/L (15). As a result of

the high costs of this protocol and introduction of nucleos(t)ide analogues, the most cost-effective approaches is tailoring the HBIG administration according to serum anti-HBs level (16) and continuation of antiviral therapy.

The main limitation in the study by of Xu *et al.* (5) was its retrospective design. Consequently, it made it impossible to compare different strategies and protocols. Finally the model that they presented for evaluating the risk of hepatitis B recurrence (MERB) was based on preoperative presence of HCC, serum HBV DNA and antiviral therapy. All of these variables were significant in multivariate analysis, but these results need to be confirmed in a prospective study with a larger sample size.

Other questions also remain unanswered. Because of limitations of the retrospective analysis, no intervention was rigorously examined. A few patients received potent antivirals such as entecavir. Another point that should be emphasized is the possibility of co-infection with hepatitis D virus (HDV) infection in HBV-transplanted patients that they did not mention in their study. Patients with co-infection of HDV/HBV are at lower risk of HBV recurrence after LTx (17). Another issue in their study was the HBsAg status after LTx: it is important to mention that positivity of HBsAg has adverse effects on graft and patient survival. Their strategy for dealing with rejection and recurrence was not clear. Did they use rituximab or not? There are some data regarding the role of this medication in re-activation of HBV infection (18). A final question is whether their patients required a second transplant or not? It can affect the outcome.

Despite these questions and limitations, this study has the advantage of being performed in a single center, the same technique was used for HBV DNA determination and viral mutations, and the clinical practice and follow up were similar. Thus, this study sheds some light on important issues surrounding liver transplantation outcomes in patients with chronic hepatitis B. The findings should be confirmed in interventional prospective studies, particularly with more potent antiviral drugs such as tenofovir and entecavir.

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