Letter to the Editor

# Safety analysis of COVID-19 vaccines in liver transplant recipients: a two-center study

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Up to know, product information for COVID-19 mRNA vaccines do not include their use in patients receiving immunosuppressive medication, since they were not included in trials (1). For the BNT162b2 mRNA vaccine, one case of otherwise totally asymptomatic elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and -glutamyl transpeptidase (GGT) serum concentrations in a liver transplant recipient has been reported after the first injection (2). In the present retrospective study, we present safety outcomes of COVID-19 vaccinations in 56 liver transplant patients from two Chinese centers vaccinated with the domestic PiCoVacc, BBIBP-CorV and ZF2001 vaccines. Thirty vaccinated physicians from the Hepatopancreatobiliary Center of Beijing Tsinghua Changgung Hospital served as control, from which 1 participant received an Ad5-nCoV vaccine. The study deadline was 2021-10-31. The observation period for adverse reactions, such as muscle pain and fatigue was 1 week, while for laboratory examinations such as liver function the follow-up period was 1 month.

PiCoVacc and BBIBP-CorV are both inactivated COVID-19 virus vaccines with a two-dose schedule and a spacing of 3 to 4 weeks, while ZF2001 is a recombinant tandem-repeat dimeric receptor-binding domain (RBD)-based protein subunit vaccine with an application of three doses over a period of 2 months. Ad5-nCoV is a viral vector vaccine applied as a single injection. *Table 1* shows the basic characteristics of the 86 participants. Adverse reactions in the liver transplant and control groups were fatigue (4, 7.1% *vs.* 1, 3.3%), local pain (9, 16.1% *vs.* 6, 20.0%), cough (1, 1.8% *vs.* 0), rhinorrhea (1, 1.8% *vs.* 0) and drowsiness (0 *vs.* 4, 13.3%), respectively. All adverse reactions were mild. Fifty-four participants had normal liver function tests within 1 month before and after vaccination. A 37-year-old patient, 70 months after transplantation due to a primary liver cancer who was receiving an anti-rejection regimen of sirolimus + mycophenolate mofetil (MMF), had liver enzyme values of ALT 72.0 U/L, AST 37.6 U/L, total bilirubin (TBIL) 13.7 μmol/L, ALP 80.0 U/L and GGT 58.3 U/L before and ALT 68.3 U/L, AST 37.7 U/L, TBIL 11.0 μmol/L, ALP 96.0 U/L and GGT 62.2 U/L after vaccination. The condition was considered to be related to the graft fatty liver and the liver function changes were not significant before and after vaccination. The second case was a 46-year-old patient with hepatic alveolar echinococcosis 30.7 months after transplantation and an anti-rejection regimen of tacrolimus + MMF. Liver enzyme values were ALT 22 U/L, AST 29 U/L, TBIL 12.4 μmol/L, ALP 134 U/L, GGT 44 U/L before and ALT 19 U/L, AST 25 U/L, TBIL 11 μmol/L, ALP 106 U/L and GGT 41 U/L after vaccination. The patient underwent a choledochojejunostomy, because of a narrow biliary anastomosis. Since there was no stenosis after the choledochojejunostomy, this abnormal ALP may be related to the state of bilioenteroanastomosis.

Two of the vaccines in the present study were inactivated viruses, which are only recommended for solid organ transplant recipients after careful risk benefit assessment,

**Table 1** Basic characteristics and vaccines of the participants

| Characteristic | Transplant group, N=56 | Control group, N=30 |
|---|---|---|
| Gender | | |
| Male | 45 | 22 |
| Female | 11 | 8 |
| Age, years, median [range] | 49 [20–67] | 40 [25–60] |
| Primary disease before transplantation | | – |
| Polycystic liver | 2 | |
| Liver cancer | 17 | |
| Wilson's disease | 1 | |
| Liver failure | 12 | |
| Hepatic alveolar echinococcosis | 2 | |
| Hepatitis cirrhosis | 19 | |
| Drug-induced liver injury | 3 | |
| Anti-rejection regimen | | – |
| MMF | 1 | |
| Tacrolimus | 12 | |
| Tacrolimus combined with MMF | 34 | |
| Tacrolimus + sirolimus + MMF | 2 | |
| Sirolimus | 1 | |
| Sirolimus combined with MMF | 6 | |
| Vaccine administration time after transplantation, months, median [range] | 32 [8–75] | – |
| At the time of vaccination | | |
| Viral hepatitis | 1 | 0 |
| Tumor recurrence | 0 | 0 |
| Vaccines received | | |
| PiCoVacc vaccine | 39 | 27 |
| BBIBP-CorV vaccine | 14 | 2 |
| ZF2001 vaccine | 3 | 0 |
| Ad5-nCoV vaccine | 0 | 1 |

MMF, mycophenolate mofetil.

because of possible allosensitization, graft rejection and/or infection (3,4). However, a meta analysis of 90 studies reporting on standard (non-COVID-19) vaccination in transplant recipients showed a similar risk of transplant rejection compared with non vaccinated controls (3). Also in the present study, no graft rejection, infection or other serious vaccine related event occurred. A major concern is the lack of neutralizing antibody development after vaccination of transplant patients. As reported in the literature older age, use of high dose prednisone in the past 12 months, MMF and triple therapy, as well as poor renal function (low estimated glomerular filtration rate) were associated with low response to the vaccine (5). However, a third booster injection did improve the initially

 

low titer and has been proposed to be incorporated into routine clinical practice (6), which is already the case for the ZF2001 vaccine. In addition, phase II trials of the BNT162b2 mRNA vaccine are under way in China, while booster injection of the inactivated vaccine is also being promoted. Liver transplant recipients will likely receive safe and effective protection from supplementary immunization and cocoon strategy.

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## Footnote

*Provenance and Peer Review:* This article was a standard submission to the journal. The article has undergone external peer review.

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-392/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Beijing Tsinghua Changgung Hospital (approval number: 21341-6-01). Donation of organs in this study reported was voluntary and with appropriate authorization or consent, and no executed prisoners served as organ donors.



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