クチン株による軽症の水痘発症の報告は散見され、水痘ワクチンの接種を受けた家族は皮疹出現に注意し、出現した場合は移植患者との接触を避ける必要がある。皮疹の好発時期は接種後3週間程度(6～43日)とされており、ワクチン株による2次感染も稀ながら報告されている[1]。ロタウイルスワクチンは生ワクチンであることから、ウイルスを排泄して患者に伝播する可能性があり、接種後は手洗いなどに注意する必要がある。ポリオについてはIPV接種を原則とする。

移植ドナーとなる患者の家族は、予防接種歴を確認してドナー本人が必要なワクチンを接種すべきである。生ワクチンウイルスについては、移植片を介した伝播の可能性が理論上はあり、接種は移植3週間前までには終了すべきである。

文献検索

CQ7 固形臓器移植患者の同居家族に推奨されるワクチンは何か。

P：固形臓器移植患者の同居家族に対して

I：予防接種を行った場合と

C：行わない場合で

O：固形臓器患者の感染予防効果に差が出るか

(solid organ transplantation or liver transplantation or kidney transplantation or heart transplantation or small bowel transplantation) and (immunization or vaccination) and (family or household)

51件中1件採用

参考文献

1) Chaves SS, Haber P, Walton K, et al. Safety of varicella vaccine after licensure in the United States : experience from reports to the vaccine adverse event reporting system, 1995-2005. J Infect Dis. 2008 ; 197 Suppl 2 : S170-7.

Serostatus Following Live Attenuated Vaccination Administered Before Pediatric Liver Transplantation

Takanori Funaki,[1] Kensuke Shoji,[1] Ippei Miyata,[1] Seisuke Sakamoto,[2] Mureo Kasahara,[2] Hironori Yoshii,[3] Isao Miyairi,[1] and Akihiko Saitoh[1,4]

[1]Division of Infectious Diseases, Department of Medical Subspecialties, National Center for Child Health and Development, Tokyo

[2]Division of Transplant Surgery, Center for Transplant Surgery, National Center for Child Health and Development, Tokyo

[3]The Research Foundation for Microbial Diseases of Osaka University, Kagawa

[4]Department of Pediatrics, Niigata University Graduate School of Medical and Dental Sciences, Niigata

Corresponding Author

Akihiko Saitoh, M.D., Ph.D., F.A.A.P.

Professor and Chairman

Department of Pediatrics

Niigata Graduate School of Medical and Dental Sciences

1-757 Asahimachi-dori, Chuo-ku, Niigata, 951-8510 Japan

Tel: +81-25-227-2222

Fax: +81-25-227-0778

E-mail: asaitoh@med.niigata-u.ac.jp

Funding

This study was supported by a grant from the Ministry of Health, Labor and Welfare of Japan (H25-Shinko-Ippan-009) awarded to A.S.

Disclosure

The authors declare no conflict of interest.

Abbreviations

live attenuated vaccines, LAVs; liver transplantation, LT; measles, mumps, and rubella, MMR; measles and rubella, MR; solid organ transplantation, SOT; white blood cell count, WBC; absolute lymphocyte count, ALC; post operative month, POM

Word Counts: Abstract 248 words, Text words 3539 words

Abstract

Background: After liver transplantation (LT) live attenuated vaccines (LAVs) are generally contraindicated. LAVs are recommended prior to LT for patients ≥6 months of age. However, the evidence supporting this practice is limited.

Methods: Patients were enrolled before and after LT. Clinical data of patients were obtained from medical records. Serum antibody titers were evaluated at the time of enrollment and prospectively. Serum antibody titers for measles and rubella were measured by hemagglutination inhibition test, and by enzyme-linked immunosorbent assay for varicella and mumps. Univariate and multivariate analyses were performed to investigate the factors that affect serostatus.

Results: Serological analyses of 49 patients immunized prior to LT (median age, 45 months; male, 35%) were performed. Underlying diseases were biliary atresia (n = 27, 55%), metabolic diseases (n = 13, 27%), fulminant hepatic failure (n = 5, 10%), and others (n = 4, 8%). The seropositivity rate after each vaccine was 46.9% (measles), 89.4% (rubella), 67.5% (varicella) and 48.8% (mumps), respectively. Factors independently associated with seronegativity were vaccination age <12 months for measles (P = 0.002), lower body weight for varicella (P = 0.013) and underlying diseases other than biliary atresia for mumps (P = 0.004). No serious adverse event was observed during the study period.

Conclusions: Immunogenicity of LAVs prior to LT was high for rubella but low for the others. Prior to LT, further vaccination strategies are needed for the patients prior. As well, serological follow-up may be indicated for patients with factors associated with seronegativity.

Introduction

Organ transplant candidates and recipients are at higher risk for infectious complications. In this particular population, vaccine-preventable diseases such as measles [1] and varicella [2] can actually be life-threatening. For these individuals, inactivated vaccines are considered safe and are usually recommended after solid organ transplantation (SOT). Live attenuated vaccines (LAVs), on the other hand, are generally contraindicated after SOT, including liver transplantation (LT) [3, 4]. Instead, SOT candidates are recommended to receive LAVs prior to transplantation [3, 4]. LAVs are generally administered to healthy children at 12 months of age or older, given that measles, mumps and rubella (MMR) vaccine is most effective after 12 months of age when maternal antibodies have waned. Furthermore, at that age, their immune function is matured enough to respond to pathogens. For pediatric SOT candidates, however, there are limited opportunities for immunization. In some cases, LAVs were administered as early as six months of age due to the timing of the transplantation [3]. The recent Infectious Diseases Society of America (IDSA) guideline states that LAVs can be administered to SOT candidates at 6–11 months of age if they are not immunosuppressed, and the transplantation is not anticipated in the ensuing four weeks. In addition, repeated doses of MMR and varicella vaccines (≥3 months apart after first administration of the identical vaccine) at 12 months of age are recommended if transplantation is delayed [4]. According to the IDSA, another important

reason to immunize patients before transplantation is that immunity acquired from the vaccine may wane due to long-term immunosuppressive therapy after LT [5-8]. While these recommendations are reasonable, the efficacy of such a practice is unclear. Moreover, it is difficult to determine which patient would be requiring additional follow-up.

The objective of this study is to evaluate the factors associated with serostatus in LT recipients who received LAVs for measles, mumps, rubella and varicella prior to LT. The focus is on patients who have undergone living-donor LT. These patients usually require less immunosuppressants than those who received cadaveric livers because of the half-matched histocompatibility between donors and recipients [9]. We hypothesized that this may be an important factor in determining the seropositivity after immunization.

Materials and Methods

Patient enrollment

Patients before and after LT at the National Center for Child Health and Development (NCCHD), the largest pediatric LT center in Japan, were enrolled. Eligibility criteria for this study were: 1) patients who received at least one LAV (measles-rubella (MR) combination vaccine, or a single-antigen vaccine licensed in Japan at the time of the study, including measles, rubella, varicella, or mumps)

prior to LT, and 2) subjects who had undergone serum antibody testing between January 2011 and June 2012. The vaccine strains were: AIK-C, Schawartz-FF8 for measles; TO-336, Takahashi, Matsuura for rubella; Oka for varicella; and Hoshino, Torii for mumps [10]. Exclusion criteria for this study include: 1) patients/parents who did not consent to the study, 2) patients who could not be followed up regularly at our institution, and 3) subjects who contracted any of the four diseases prior to or during this study.

Institutional vaccine administration protocol

Vaccines were given to patient before transplantation according to the national immunization program in Japan [11] to maximize the immunization opportunity for each patient. LAVs were administered at least four weeks prior to LT. Inactivated vaccines were administered at least two weeks prior to LT [12]. Administration of LAVs is generally recommended at one year old; however, it is acceptable to administer measles vaccine as early as six months of age in the event of an outbreak. Vaccines were administered either sequentially (one by one) or simultaneously because simultaneous vaccination was still not widely accepted in Japan during the study period [13]. When LAVs were given sequentially, no specific order was set. According to the Japanese Immunization Law, there must be a four-week period between each immunization.

Blood sampling

Blood samples were collected from the study participants. At each post-LT follow-up, an additional 2–3 mL of blood was collected at the outpatient clinic. The blood samples were centrifuged and the separated plasma samples were stored at -20°C until analysis.

Immunosuppression after LT

Tacrolimus and low-dose corticosteroids were used for initial immunosuppression. Tacrolimus administration commenced on the day of LT. The target whole blood trough level of tacrolimus was 10–12 ng/mL for the first two weeks, approximately 10 ng/mL for the following two weeks, and 8–10 ng/mL thereafter. Corticosteroid was tapered from 1.0 mg/kg/day to 0.3mg/kg/day during the first month, and was withdrawn within the first three months. Mycofenolate mofetil was administered when patients show tacrolimus-associated side effect or steroid resistant refractory rejection [14].

Data collection

The following characteristics of the study subjects were obtained from the medical records and analyzed: age, gender, body weight, underlying diseases, date of LT, past medical history of measles, rubella, varicella, mumps and vaccination records, and adverse events and reactions after LAVs. Blood was collected at the time of enrollment. Subsequently, blood was collected depending on the availability of the patients. Serum antibody titers for measles (hemagglutination inhibition [HI] test), rubella (HI), varicella (glycoprotein enzyme-linked immunosorbent assay [gpELISA]) [15], and

mumps (enzyme-linked immunosorbent assay [ELISA]) were evaluated at the Research Foundation for Microbial Diseases of Osaka University. Serostatus was determined using the following antibody cutoff levels for each pathogen: measles, 8 IDU (interdilution unit); rubella 8, IDU; varicella, 50 EU (ELISA unit); and mumps, 400 EU. Adverse reactions or events within four weeks of immunization were evaluated using the medical records.

Statistical analysis

Statistical analysis was performed using the SPSS 21.0 software package (SPSS, Inc., Chicago, IL). Categorical variables were compared using the Fisher's exact test or the chi-square test and continuous variables were compared using the Mann-Whitney's U-test. Independent factors associated with seropositivity were analyzed using multivariate analysis and included factors with a P-value <0.10 by the univariate analyses. P-values <0.05 were considered statistically significant.

Ethics

Written informed consent or assent for the use of personal medical information and the participation of the study was obtained from all patients and/or their parents. This study was approved by the Institutional Review Board of the NCCHD and was performed in compliance with the guidelines set forth by the institutional review board at the NCCHD.

Results

Patients' characteristics

Among 84 patients who agreed to participate in the study, 11 with past medical history of varicella and four with past history of mumps were excluded. Unvaccinated patients (measles and rubella: 26, varicella: 24, and mumps: 30) were also excluded. Finally, a total of 49 patients were enrolled in the study. A diagram summarizing patients' enrollment and blood specimen sampling is shown in **Supplementary Figure 1**.

Nearly all enrolled patients (47/49, 96%) received living-donor LT; the other two patients received cadaver-donor LT. The number of patients who received LAVs prior to LT was 49 for measles, 48 for rubella, 40 for varicella and 41 for mumps (**Table 1**). Forty-four (90%) patients were given measles vaccine first. Of these patients, 20 were simultaneously administered with rubella vaccine, three with rubella and varicella vaccines, and 10 with rubella, varicella and mumps vaccines. Meanwhile, 5/49 (10%) patients were given varicella vaccine first, and two of them were simultaneously administered with mumps vaccine. The median age of patients at the time of blood collection was 45 months and the median time after LT was 20 months. The major underlying diseases included biliary atresia (55%), metabolic disorders (e.g. glycogen storage disease type 1b, propionic acidemia, ornithine

transcarbamylase deficiency) (27%) and fulminant hepatic failure (10%). At the time of blood sampling, more than 75% of the patients were receiving tacrolimus as the only immunosuppressant.

Factors associated with seropositivity for each live attenuated vaccine

Measles

Seropositivity for measles vaccine evaluated by specimens collected at a median of 21 post-operative months was 46.9% (23/49) (**Table 2A**). Univariate analysis identified age (P = 0.003), body weight (P = 0.004), age at vaccination (≥12 months) (P = 0.001) and age at transplantation (P < 0.001) as potential factors associated with seropositivity for measles. Higher serum tacrolimus trough concentration (P = 0.023), a lower white blood cell count (WBC) (P = 0.001) and a lower absolute lymphocyte count (ALC) (P = 0.001) were also significantly associated with seropositivity. A multivariate analysis including these factors associated with serostatus demonstrated that the age at vaccination (≥12 months) was the only independent factor related to seropositivity for measles after pre-transplantation vaccination (**Table 3A**).

Rubella

Seropositivity for rubella vaccine evaluated by specimens collected at a median of 19 post-operative months was 89.4% (42/48) (**Supplementary Table 1**). Seropositive rate was similar after LT. Univariate analysis demonstrated the type of underlying diseases associated with serostatus (P =

0.009). A multivariate analysis did not demonstrate significant factors associated with serostatus of rubella vaccine.

Varicella

Seropositivity for varicella vaccine evaluated by specimens collected at a median of 18 post-operative months was 67.5 % (27/40) (**Table 2B**). Univariate analysis demonstrated that age ($P < 0.001$), body weight (($P < 0.001$), vaccination age ($\geq$ 12 months) ($P = 0.007$), age at transplantation ($P = 0.007$) and time from the latest vaccination ($P = 0.003$) were associated with seropositivity. In addition, lesser immunosuppressants ($P = 0.032$), higher serum tacrolimus trough concentration ($P = 0.001$) and lower ALC ($P = 0.018$) were also significantly associated with seropositivity. Multivariate analysis including these significant factors demonstrated body weight at vaccination ($\geq$12 months) to be an independent factor related to seropositivity ($P = 0.013$) **(Table 3B)**.

Mumps

Seropositivity for mumps vaccine evaluated by specimens collected at a median of 19 post-operative months was 48.8% (20/41) (**Table 2C**). Seropositive rate was similar after LT. Univariate analysis demonstrated that underlying diseases ($P = 0.026$) and lower number of immunosuppressants ($P = 0.046$) were associated with seropositivity. The majority of patients (80%) with biliary atresia as their underlying disease was seropositive and was statistically significant after multivariate analysis

(P = 0.004) (**Table 3C**). Patients who were seronegative for mumps were more likely to have metabolic disorders as their underlying disease (9/21, 42%, P = 0.085).

Changes in antibody levels in patients whose sequential data were available

We further analyzed the sequential antibody data in patients whose subsequent antibody levels after LT were available. The median post-operative months of the 1st and 2nd blood sampling after LT were as follows: measles and rubella (n = 16, 25 and 37, respectively), varicella (n = 15, 24 and 35, respectively), and mumps (n = 13, 24 and 35, respectively). Seropositivity rates for each vaccine were as follows: measles (44% to 56%), rubella (81% to 100%), varicella (73% to 80%), and mumps (62% to 23%), demonstrating that high seropositivity maintained in rubella and varicella vaccines, in contrast, seropositivity decreased significantly in mump vaccine.

Additionally, we further analyzed sequential antibody data in six patients whose antibody levels were available before LT and after LT. The median post-operative months of 2nd blood withdraw was 6 post-operative months (range: 5-15 months). The changes in antibody levels before LT and after LT for each vaccine are shown in **Figure 1**, demonstrating that antibody levels of mumps vaccine tend to decrease gradually in all patients; however, the changes in antibody levels of measles, rubella and varicella varied in each individual.

Difference in seropositive rates between patients who received vaccination at <12 months and at ≥12months

In general, the recommended age for LAVs administration in healthy patients was ≥12 months. With an age cutoff of 12 months, the difference in seropositivity for each disease was evaluated. The rates of seropositivity after LAVs at the age of < 12 months and ≥12 months were as follow: measles, 12.5% and 63.6% (P = 0.001); rubella, 83.3% and 93.1% (P = 0.357); varicella, 44.4% and 86.4% (P = 0.007); and mumps, 46.6% and 50.0% (P = 1.000) (**Figure 2).**

Adverse events or reactions

There was no obvious adverse reaction or event after pre-LT LAVs administration, except for one patient who developed a self-limited episode of fever seven days after MR vaccination. In addition, no critical adverse reactions or post-transplant issues related to the administration of LAVs were recorded.

Discussion

We investigated the factors affecting the seropositivity of measles, rubella, varicella, and mumps vaccines given to patients prior to LT. Rubella vaccine administration prior to LT was associated with a relatively high rate of seropositivity even after LT. On the other hand, the other LAVs were

suboptimal compared to healthy patients who demonstrated a sustained seropositivity of greater than 90% [16]. To our knowledge, this is the first report, consisting mainly of living-donor LT recipients, that evaluated the factors associated with seropositivity of LAVs given prior to LT. We found that the independent factors associated with seropositivity in patients who received LAVs were age at measles vaccination (≥12 months or <12 months), body weight at the time when varicella titer was tested, and patient's underlying disease for mumps vaccine.

After LT, LAVs are generally contraindicated because of the risk of the attenuated vaccine strain developing into a disease itself instead of conferring immunity under the immunocompromised status. Our findings demonstrated that vaccine failure is common in LT recipients, particularly when vaccines are administered before 12 months of age. An early literature reported that while seroconversion rates after pre-transplantation vaccination against LAVs were all above 80%, secondary vaccine failures ensued with a rapid loss of seroconversion in LT recipients within 12 months [8]. The reported seroconversion rates one year after LT were similar to our results obtained at approximately 20 months after LT. Thus, after LT, the serostatus should be followed up in patients who received LAVs before LT. In the current study, measles vaccination at age <12 months was found to be an independent factor associated with vaccine failure. This is likely due to the presence of maternal antibodies that can interfere with LAVs resulting in primary vaccine failure [17]. In

contrast, one study suggested that rate of seroconversion after measles vaccination prior to LT was relatively high (82%); however, it gradually waned after LT [8]. According to a study in Taiwan, where the first measles vaccine is given at nine months of age, the seroconversion rate after measles (84.0%), rubella (82.0%) and varicella vaccination (74.0%) in patients with biliary atresia before LT without immunosuppression was significantly lower than the normal population with standard vaccine schedule (96.7%, 98.7%, and 95.3%, respectively) [18]. Some guidelines and reports recommend that infants who are likely to undergo transplantation should receive their first dose at six months of age and a second dose at 12-15 months of age [4, 12]. Another study; however, reported that an early vaccination age might increase the risk of varicella vaccine failure [17]. In the current study, vaccination age was not independently associated with vaccine failure.

With the exception of rubella vaccine, serum trough level of tacrolimus was higher in seropositive patients than in seronegative patients in the current study. This counterintuitive finding is likely to be attributed to the overriding effect of age and a presence of other co-founders, given that multivariate analyses did not show that a high trough level of tacrolimus was significantly associated with serostatus. In addition, univariate analyses showed counterintuitive data that low ALC was associated with seropositivity for measles and varicella; however, multivariate analyses did not show the factor was not significantly associated with seropositivity. We speculated that cellular

immunity was strongly involved in the acquisition and maintenance of protective antibody. In the current study, the parameters reflecting cellular immunity such as T-lymphocyte counts, CD4/CD8 ratio, and lymphocyte blastoid transformation were not evaluated for the interpretation of the counterintuitive finding. Therefore, a further prospective study that examines virus-specific cell-mediated immunity is needed to elucidate the relationship between ALC and cellular immunity. In this study, a lower body weight was the only factor independently associated with vaccine failure in patients who received pre-LT varicella vaccination. As the body weight represents the nutrition status of a patient, it may influence the immune response to vaccination, although there are many other factors associated with immunization response. A meta-analysis has described the relationship between poor nutritional status and impaired serologic response to inactivated hepatitis B virus vaccine in patients with chronic kidney diseases [19]. There are also intriguing reports on how the potential of nutrition-dependent adipocyte-derived hormones can affect the induction and maintenance of pro-inflammatory T helper 1 immune response [20-22]. According to the multivariate analysis, we found that a seronegative status after mumps vaccination was independently associated with underlying diseases other than biliary atresia. In particular, patients who were diagnosed with metabolic diseases were likely to be seronegative for mumps vaccine after pre-transplant vaccination. A clear explanation for this remains elusive. It may be possible that

metabolic diseases influence the nutritional status. However, no previous report has described the relationship between nutritional status and immune response after LAVs in transplant recipients. A relationship of such nature was not evaluated in the current study either. While it was interesting that different factors appeared to be predictive of the serostatus of vaccines, the explanation for that is extremely complicated because many factors are contributing to the antibody levels, including age, immunological and nutritional status, differences in vaccine formulations, underlying diseases, the differences in the histocompatibility between donors and recipients [9] and cellular immunity. These factors may also affect the sequential antibody data in patients after LT because sequential serostatus of each vaccine varied significantly. Unfortunately, in the current study, we were unable to evaluate some of these factors. We believe that further studies with a focus on the role of cellular immunity may provide the answers.

We acknowledge that there are several limitations to our study. First, this study was performed in a single institution and almost all the patients were Japanese. Therefore, ethnic variation should be considered before applying the findings of the current study to populations of different race and ethnicity. In addition, a few inherent issues related to the immunization system in Japan, such as a lack of MMR vaccine and the use of domestic strains of mumps vaccine, may have potentially affected the current study [23]. Second, cellular immunity such as varicella-zoster