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Research Article / Araştırma Makalesi

Administration of Attenuated Live Vaccines Before and After Liver Transplantation in Childhood: Single Center Experience in Turkey

Çocukluk Yaş Grubunda Karaciğer Nakli Öncesi ve Sonrası Zayıflatılmış Canlı Aşı Uygulamaları-Türkiye'den Tek Merkez Deneyimi

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Abstract

The aim of this study was to evaluate the attenuated live vaccine administration before and after liver transplantation. This study was carried out at the Child Health Surveillance Unit of the Social Pediatrics Department. Besides healthy children, children with special needs are being followed-up at the Unit. Each child has a personal health record in the unit. The health records of patients who had received attenuated live vaccine before liver transplantation under 1 year of age or after liver transplantation were evaluated. Demographic characteristics, data showing immunologic status before vaccination, vaccine related reactions and serologic responses were obtained from health records of each child. Retrospective files of 5 patients who were in follow-up were examined. Four patients at least 2 years after the liver transplantation had attenuated live vaccination (measles-mumps-rubella vaccine and / or chickenpox vaccine). No adverse reaction was noted after the immunization among these 4 children. A 6-month-15-day-old infant who was a candidate for liver transplantation had been vaccinated with measles-mumps-rubella and chickenpox vaccine and it was determined that the serological response after vaccination was not complete in the baby who did not have any adverse reactions after vaccination. Our findings demonstrated that despite the use of immusuppressive therapy, it is safe to apply attenuated live vaccines after the transplantation if appropriate conditions were provided. The timing of the rapid effective immunization before transplantation under one year of age needs to be further investigated.

Keywords: Child, liver transplantation, attenuated live vaccination

Özet

Karaciğer nakli öncesi ve sonrası çocuklarda canlı aşı uygulamalarının değerlendirilmesidir. Çalışmamız Sosyal Pediatri Bilim Dalı Çocuk Sağlığı İzlem Birimi'nde yapılmıştır. Birimde sağlıklı çocukların yanı sıra özel ihtiyaçları olan çocuklar da takip edilmektedir. Birimde takipli her çocuğun sağlık kaydı bulunmaktadır. 1 yaşın altında karaciğer nakli öncesinde veya karaciğer nakli sonrasında zayıflatılmış canlı aşı almış hastaların sağlık kayıtları değerlendirildi. Her çocuğun sağlık kayıtlarından demografik özellikler, aşılama öncesi immünolojik durumu gösteren veriler, aşı ile ilgili reaksiyonlar ve serolojik yanıtlar kaydedildi. Takipte olan 5 hastanın geriye dönük dosya incelemendi. Bunlardan dördüne nakilden en erken 2 yıl sonra olmak üzere zayıflatılmış canşı aşı (kızamık-kızamıkçık-kabakulak ve/veya suçiçeği aşıları) uygulanmıştır. Bu dört hastanın hiçbirinde aşı sonrası bir sorun gelişmemiştir. Nakil öncesi zayıflatılmış canlı aşı uygulanan 6 ay 15 günlük bebekte kızamık- kızamıkçık-kabakulak ve suçiçeği aşıları uygulanmıştır. Aşı sonrası herhangi bir istenmeyen reaksiyon gözlenmeyen bebekte aşı sonrası serolojik yanıtın tam olmadığı belirlenmiştir. Bulgularımız nakil sonrası immunsüpresif kullanmakta olan çocuklarda gerekli değerlendirmeler sonrasında zayıflatılmış canlı aşı uygulanmasının güvenli olduğunu ortaya koymaktadır. Diğer yandan karaciğer nakli planlanan, acil aşılanması gereken 1 yaş altındaki hastalarda KKK ve suçiçeği aşı uygulamaları sonrası yeterli yanıt oluşması konusunda ayrıntılı değerlendirme gerekmektedir.

Anahtar Kelimeler: Çocuk, karaciğer nakli, canlı aşılama

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1. Introduction

Generally, inactive vaccine administrations are continued 2-6 months after the transplantation depending on their conditions, and if they have not been vaccinated previously, a new vaccine schedule is established (1). However, there are various approaches for live vaccine administration after solid organ transplantation. This is due to the lifelong use of immunosuppressive drugs (2-5). Recently, the suggestions supporting attenuated live vaccine (ALV) administration after solid organ transplantation have started to take place in the literature (6-11).

It is reported that the patients under 1 year of age can have attenuated live vaccination during the preparation stage of solid organ transplantation (1,3). On the other hand, there are different opinions regarding the optimal timing of vaccination, particularly considering maternal antibodies (12-14).

This article aims to present the results of ALV administration in post-transplant 4 patients and in a pre-transplant infant.

2. Methods

An average of 25 patients are transplanted annually in the İstanbul Faculty of Medicine Department of Pediatrics Division of Pediatric Gastroenterology, a leading center for pediatric liver transplants in Turkey both living organ transplantation and, less frequently, cadaver transplantation are performed in the Liver and Biliary Tract Surgery unit of this center. The transplant preparations of patients who are followed up by the İstanbul Faculty of Medicine Division of Pediatric Gastroenterology and for whom liver transplantation is decided due to chronic liver disease are carried out in cooperation with several medical departments. These patients are also monitored by the İstanbul Faculty of Medicine Department of Pediatric, Division of Social Pediatrics for age-appropriate vaccination. An individual patient file is created for these children, past vaccinations are evaluated, an age- appropriate vaccination scheme is established. A follow up programme is organized for this purpose. Except for particular cases, transplant patients receive methylprednisolone for the first 3 months, and on tacrolimus immunosuppression immediately after the transplant for lifelong period. The patient is followed up by the gastroenterology department and the transplantation unit every month for the first 6 post-transplantation months, and at gradually increasing intervals after that. Immunosuppressive drug levels are regularly controlled, and doses are adjusted accordingly. The tacrolimus dose is generally planned as 8-10 ng/mL in the acute period, 5-10 ng/mL in the subsequent period, and 3-5 ng/mL after the first year, where the dosage is adjusted according to clinical condition (15). After the transplant, the Division of Social Pediatrics establishes a vaccination schedule for the remaining vaccines. If necessary, ALV administrations are included in the schedule after consulting with the Department of Pediatric Immunology.

A personal health record is available for every patient who is followed-up by the Division of Social Pediatrics for vaccination before or after transplantation. A detailed history is taken, and physical examination is performed at each encounter. Any contraindications for ALV after transplantation is evaluated according to the criteria (Table 1) developed by Shinjoh et al (7). Serological condition is evaluated both before and after ALV. The patient's family is informed in detail to obtain consent prior to immunization. Families were informed about vaccine reactions (erythema, swelling, pain, rash and fever) and they were asked to call our unit if any of these reactions occur. After vaccination, patients are closely monitored, and any problems or rejection are evaluated and recorded. All evaluations are made by a multidisciplinary team consisting of the Divisions of Social Pediatrics, Pediatric Immunology, and Pediatric Gastroenterology.

Table 1. Eligibility criteria for the attenuated vaccination after liver transplantation (7)

1. Positive intention of the family for vaccination of the child and the approval of the unit which follows up the patient.
2. ≥ 2 years after liver transplantation
3. Borderline or negative serological value for any measles, mumps, rubella and/or varicella infections
4. Tacrolimus level <5 ng/mL or cyclosporine level <100 ng/mL
5. Not using IVIG, steroid (>0.2 mg/kg/day) or having blood product for the last 6 months
6. Normal serum levels of liver enzymes (AST, ALT) total bilirubin, and no rejection finding within the last 6 months
7. Evaluation of humoral and cellular immunity;
    a. IgG >500 mg/dL
    b. Total lymphocyte count >1000/ µL or children ≥ 6 years of age and >1500/ µL for those younger than 6 years
    c. CD4 >700/ µL for < 6 years of age, and >500/ µL for 6 years old and older
    d. CD4/CD8 >1
    e. Normal proliferation test

In this study, we retrospectively evaluated the patients' files in the Division of Social Pediatrics. The results of measles-mumps-rubella (MMR) and / or chickenpox vaccinations to 4 patients who have underwent liver transplantation more than 2 years ago, and to a patient younger than 1 year of age before transplantation were evaluated. We recorded the reasons for transplantation, the timing of transplantation, vaccination status before the transplantation, the timing of ALV administration after the transplantation, the biochemical results, pre- and post-vaccination serologic responses, any local or systemic reactions, and the follow-up duration. The Enzyme Linked Immunosorbent Assay (ELISA) was used to evaluate serological responses at least 1 month after vaccination.

The İstanbul Faculty of Medicine local ethical committee approved the study (ethics committee decision number: 2020/323).

3. Results

According to the retrospective evaluation of patient files between October 2018 and February 2020 in the Social Pediatrics Outpatient Clinic, ALV administered to 5 patients before or after liver transplantation. The characteristics of our patients are summarized in Table 2.

All patients are still under follow-up by our clinic. The ages of the patients at the time of ALV administration are presented in Table 2. Three patients had living-donor transplantations and 1 had a cadaver transplantation, and at least 2 years had passed form the transplantation to the time of vaccination. All patients were using tacrolimus for immunosuppression, and two consecutive measurements of tacrolimus were <5 ng/mL at the time of vaccination. The patients had not received intravenous Ig (IVIG), steroids, blood products, Rituximab or mikofenolat mofetil (MMF) nor had a history of rejection within the past 6 months. Liver enzyme levels (AST, ALT), total bilirubin, total lymphocyte count (<1500/µL for <6 years old, >1000/µL for >6 years old), lymphocyte subgroups, and lymphocyte proliferation test results were normal and IgG was >500 g/dL.

The case 1 underwent liver transplantation due to Crigler–Najjar syndrome type 1 at one year of age and had received all vaccinations until that time. The patient tested negative for measles IgG and the family wished their child to be vaccinated with measles vaccine, therefore, the patient underwent the examinations presented in Table 1 and assessed for serological condition. Since the patient was measles seronegative, and the conditions were favorable, MMR vaccine was administered because a single measles vaccine was not available at the time of the administration. The patient did not develop a reaction after vaccination. The patient has been followed up for 17 months after vaccination and for 20 months in total.

Table 2. Characteristics and vaccination status of patients

	Case 1*	Case 2*	Case 3*	Case 4*	Case 5**
Gender	F	F	M	M	M
Application age (year)	9 + 5/12	4	9+10/12	9+6/12	3 months
Measles vaccine administration status before transplantation/number of dose	+/1	-	+/1	+/1	-
Rubella vaccine administration status before transplantation/number of dose	+/1	-	+/1	+/1	-
Mumps vaccine administration status before transplantation/number of dose	+/1	-	+/1	+/1	-
Varicella vaccine administration status before transplantation/number of dose	+/1	-	-	-	-
Reason for transplantation	Crigler–Najjar syndrome type 1	Biliary atresia	Fulminant hepatitis	Biliary cirrhosis	Methylmalonic acidemia
Type of liver transplantation	Living donor	Living donor	Cadaver	Living donor	-
Age at transplantation (year-month)	1 year	9 months	4 years	1 year	-
Time passed after transplantation at the time of vaccination (year)	8	3	5	8	NA
Evaluations at the application					
Measles IgG	Negative	Negative	Positive	Negative	NA
Rubella IgG	Positive	Negative	Positive	Positive	NA
Mumps IgG	Positive	Negative	Positive	Negative	NA
Varicella IgG	Positive	Negative	Negative	Positive	NA
AST (U/L)	24	34	35	34	NA
ALT (U/L)	15	22	25	20	NA
Total bilirubin (g/dL)	1.2	0.66	0,26		NA
IgG (mg/dl)	814	1095	1282	1385	NA
Total leukocyte count-absolute lymphocyte count /µL	10.300 -3300	5710-2500	6600-2700	9400-3290	NA
Lymphocyte subgroups					NA
CD4 (%) - CD8 (%)	32 – 25	38 - 23	28 - 21	42 - 18	NA
CD4/CD8	>1	>1	>1	>1	NA
Lymphocyte proliferation test	Normal	Normal	Normal	Normal	NA
Tacrolimus level (2 sequential value) (ng/mL)	4,9 – 4,6	4,3 – 3.9	4 – 3,7	3.1 -3,7	NA
Administered vaccine					
MMR	+	+	-	+	+
Varicella	-	+	+	-	+
Evaluation after vaccine administration					
Measles IgG	Positive	Positive	NA	-	Negative
Rubella IgG	NA	Positive	NA	NA	Negative
Mumups IgG	NA	Negative	NA	-	Positive
Varicella	NA	Negative	Negative	NA	Negative
Local/systemic reactions after vaccination	Not observed	Not observed	Not observed	Not observed	Not observed
Antibody evaluation time after vaccination (month)	3	3	1-2	1,5	5,5
Total duration of follow up time (month)	20	17	16	15,5	15,5
Follow up after vaccination (month)	17	9	4	1,5	12

**: Posttransplant; **:Pretransplant; M:Male; F: Female; NA: Not available; MMR: Measles-Mumps-Rubella*

The case 2 had biliary atresia and underwent a Kasai procedure at 2 months of age and liver transplant at 9 months. The patient had not received MMR or varicella vaccines before the transplant and tested negative for varicella IgG, measles IgG, rubella IgG and mumps IgG. The family wished their child to be vaccinated; therefore, the patient underwent the examinations presented in Table 1 and had favorable results. She received the MMR vaccine immediately, and varicella vaccine one month later. The patient did not develop a reaction after the vaccinations. Three months after vaccination, the patient tested negative for varicella IgG and mumps IgG. It was decided to administer a second dose to the patient before the transplantation. However the consecutive tacrolimus measurements were not favorable, and the patient was put on follow up for appropriate tacrolimus levels. The patient has been followed up for 9 months after vaccination and for 17 months in total.

The case 3 underwent liver transplantation at the age of 4 years due to fulminant hepatitis. The patient tested negative only for varicella IgG and the family wished the patient to be vaccinated. Subsequently the patient underwent the examinations presented in Table 1. The patient had the varicella vaccination. The patient did not develop a reaction after vaccination. The 1-month and 2-month assessments revealed that the patient was seronegative for varicella. The patient has been followed up for 4 months after vaccination and for 16 months in total. A second dose of varicella vaccine was currently planned for the patient who was not immunized against varicella prior to transplantation.

The case 4 underwent liver transplantation at the age of one year due to biliary cirrhosis. The patient tested negative for measles IgG and mumps IgG and underwent the examinations presented in Table 1. The patient received an MMR vaccine and did not develop a reaction after vaccination. The patient was to be assessed for mumps IgG and measles IgG 1.5 months after vaccination; however, parents decided to defer serological assessment. The patient has been followed up for 15 months after vaccination and for 1.5 years in total.

The case 5 is followed up with the diagnosis of methylmalonic acidemia. MMR and varicella vaccines were administered to the patient at the age of 6 months and 15 days for rapid vaccination before transplantation. The patient did not develop a reaction after the vaccinations. The patient was kept on follow-up and had not underwent a transplantation at 12 months of age. The patient was subsequently evaluated to decide for re-vaccination and tested negative for measles IgG, rubella IgG, and varicella IgG. The patient received second doses of MMR and varicella at 12 months of age. The patient did not develop a reaction after the second doses of vaccines. The patient has still not transplanted. The patient has been followed up for 12 months after vaccination and for 15.5 months in total.

4. Discussion

Today, children with chronic diseases are more likely to survive with the available treatment options. This makes it even more important to vaccinate these children. Further studies are needed in this context, particularly regarding live vaccinations. This article presents the experiences of a leading children's liver transplantation center from Turkey regarding ALV administration before and after transplantation. ALV was administered to a total of 5 cases as per certain criteria and none of them developed any vaccine-related issues.

The World Health Organization reported an increasing prevalence of measles in Europe according to 2019 data, with 2666 cases in Turkey (16). The most effective way to prevent measles infections is vaccination. The Expanded Programme for Immunization of Turkey recommends administering the measles, mumps, and rubella vaccine in two doses at 12 months of age and at 6 years, and the varicella vaccine as a single dose at 12 months. As of November 2019, the measles vaccine was added to the program at 9 months

of age (17). Rubella immunization is very important especially for females at reproductive age due to the risk of congenital rubella syndrome (5). Viral infections can be more severe in patients who are on immunosuppressive therapy compared to healthy individuals. For these reasons, immunization is important for vaccine-preventable diseases.

Although ALV administration is generally considered to be contraindicated after solid organ transplantation, it has long been reported that varicella vaccine can be administered after at least 2 years after transplantation and if there is no evidence of rejection or graft-versus-host disease (GVHH). Recent studies started to report that ALV administration is safe for post-transplantation patients (6,7,11).

Shinjoh et al. reported that several criteria should be taken into consideration for ALV administration after solid organ transplantation (7). These criteria included the evaluation of cellular and humoral immunity, and identification of the most favorable conditions where immunosuppression was at the lowest level. We considered these criteria for our transplant patients and administered the vaccines if all criteria were met (Table 1). Shinjoh et al. indicated that blood tacrolimus should be <5ng/dL and at least 2 years must have passed after transplantation before vaccination. Kawano et al. accepted the time of 1 year to pass after transplantation as the criterion for vaccination (8). Another publication recommends waiting for at least 1 year after transplantation and to ensure that two consecutive tacrolimus values are <8 ng/mL and that at least 2 months have passed after rejection findings (11). Since the recommendatory article of Suresh et al. was published after the establishment of vaccination schedules of our patients, our vaccine administrations were carried according to the criteria defined by Shinjoh et al. Together with the criteria included in this assessment, we included having two consecutive measurements of tacrolimus <5ng/mL and not having a history of blood product administration in the last 6 months as additional criteria. Blood product administration has been determined as an additional criterion since it affects the efficacy of the parenteral ALV administration.

Guidelines indicate that MMR and varicella vaccines can be administered at 6-11 months (1,3,18). However, there is no clear consensus on timing. A study by Ganz et al. demonstrated that neutralizing antibody levels were lower in patients where the first dose of measles vaccine was administered at the age of 6 months compared to 9 months and 12 months (13). In a study from our unit Devecioğlu et al. reported the seropositivity rates of mothers for measles, mumps, rubella, and varicella at the first month after birth as 95.7%, 92.8%, 92.8% and 96.7%, respectively. Furthermore, during the first month of life, 88% of children were seropositive for measles, 81.7% for mumps, 89% for rubella, and 96.7% for varicella whereas at six months, this ratio was 25% for measles, 14.6% for mumps, 23.2% for rubella, and 17.1% for varicella (13). Karaayvaz et al. reported the prevalence of measles seropositivity as 72.5% in cord blood, 2.6% at six months, and 3.6% at 9 months (19). Lochlainn et al. stated that a high seropositivity rate was achieved with the administration of the second dose after the first measles-containing vaccine dose which was administered before 9 months of age (20). On the other hand Princi et al. also proposed that antibody response was lower in patients who were vaccinated before 9 months compared those who were vaccinated after 9 months (21). In our study, the antibody levels of Case 5 assessed after 5.5 months indicated that the vaccine had provided partial seroconversion. This may raise the question regarding the earliest and most appropriate time for rapid vaccination under one year of age and the need for maternal antibody determination before vaccination. Nevertheless, each patient should be individually assessed, and it should be considered that a live vaccine can be administered until 4 weeks before transplantation when establishing a vaccination schedule.

Our study reflects data from a single center. The major limitation of the study is the small

number of subjects. However, it offers important data that can be used in this context.

We conclude that ALV administration is possible in patients with liver transplantations at an immunologically appropriate time. It is also important to complete immunization rapidly by a live vaccine at the earliest possible time before transplantation while considering the presence of maternal antibodies. Since our study is the first publication from Turkey reporting the administration of ALV after liver transplantation, we believe our findings will shed light on future administrations performed in other centers.

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