Live Virus Vaccination Following Pediatric Liver Transplantation: Results from Two Academic Children's Hospitals

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Background

- Live virus vaccination (LVV), including Varicella (VZV) and Measles, Mumps, and Rubella (MMR) vaccinations, is discouraged in most solid organ transplant (SOT) recipients
- Single center studies have demonstrated safety and preliminary efficacy of LVV in certain SOT populations.
- At our two centers, LVV has been given to some orthotopic liver transplant (OLT) patients for the past twenty years
  - Children's Hospital of Philadelphia allows for LVV so long as the patient is on one immunosuppressive (IS) agent for at least six months
  - Lurie Children's allows for LVV so long as the patient is on one IS agent

Research Objectives

- Evaluate the frequency of LVV following OLT within a pediatric cohort at two academic children's hospitals
- Compare characteristics of those who received LVV following OLT to those that did not, including level of immunosuppression at the time of LVV as well as at two year follow up
- Evaluate the incidence of adverse events attributable or associated with LVV following OLT
- Evaluate the incidence of Varicella, Measles, Mumps, or Rubella following OLT in those who received LVV post-OLT compared to those who did not

Methods

Inclusion:
- Patients undergoing OLT between Jan 2007 and Dec 2017 at Lurie Children's in Chicago and Children's Hospital of Philadelphia
- ≥ 2 years of follow up
- Documentation of any vaccination (excluding influenza) prior to OLT

Endpoints:
- Adverse events (AEs) within two weeks of receipt of LVV
- Factors that might influence the selection of patients for LVV: choice, dose, frequency, and levels of immunosuppressive (IS) medications.

Analysis:
- Age at transplant and days post-OLT that LVV was given was compared in those that received their first LVV post-OLT and those who were re-vaccinated with LVV post-OLT using Nonparametric Median Comparison
- IS in non-vaccinated patients was compared to vaccinated patients at two year post-transplant follow-up in all cohorts using Chi-Square analysis

Results

Table 1. Characteristics of OLT Recipients

Characteristics of OLT Recipients	
Patients undergoing transplantation during study period, N	307
Patients that did not qualify for study, N (%)	58 (18.8)
Patients without documented vaccinations, N (%)	12 (3.9)
Patients with non-OLT related transplant, N (%)	16 (5.2)
Incomplete records, N (%)	42 (72.4)
Patients undergoing transplantation who met study criteria, N	249
Patients with ≥1 OLT, N (%)	15 (6)
Female, N (%)	108 (43)
Care at Lurie Children's Hospital, N (%)	120 (48)
Age at first transplant, Mean (Median) in years	4.67 (1.93)
Indication for First OLT	
Biliary Atresia, N (%)	104 (41.8)
Metabolic Disease, N (%)	52 (20.9)
Liver failure of Unknown Etiology, N (%)	23 (9.2)
Autoimmune Hepatitis, N (%)	9 (3.6)
Hepatoblastoma, N (%)	8 (3.2)
Liver failure secondary to infectious etiology, N (%)	2 (0.8)
Wilson's Disease, N (%)	1 (0.4)
Other, N (%)	50 (20.1)
Patients receiving ≥1 LVV pre-OLT, N (%)	133 (53.4%)
VZV, N (%)	128 (51.4)
MMR, N (%)	129 (51.8)
Patients receiving ≥1 LVV post-OLT, N (%)	96 (38.5)
VZV, N (%)	92 (36.9)
MMR, N (%)	91 (36.5)

Table 2. Adverse Events Associated with LVV

Adverse Events	
Patients with 1st LVV given after OLT	
VZV vaccine, N of AEs (% of vaccinated pts)	2 (3.7)
Injection site reaction	1
Localized rash	1
MMR vaccine, N of AEs (% of vaccinated pts)	2 (3.4)
Injection site reaction	1
Rejection episode	1
Patients with history of ≥1 LVV prior to OLT	
VZV vaccine, N of AEs (% of vaccinated pts)	1 (2.6)
Fever post-vaccination	1
MMR vaccine, N of AEs (% of vaccinated pts)	1 (3.1)
Fever post-vaccination	1

Table 3. IS Regimens in OLT Recipients

Immunosuppressive regimens of OLT Recipients		
Number of immunosuppressive medications at time of LVV	1	>1
Patients with 1st LVV given after OLT		
VZV vaccine, N (%)	43 (81.1)	10 (18.9)
MMR vaccine, N (%)	46 (80.7)	11 (19.3)
Patients re-vaccinated after OLT		
VZV vaccine, N (%)	33 (86.8)	5 (13.2)
MMR vaccine, N (%)	29 (90.6)	3 (9.4)
Number of immunosuppressive medications 2 years after OLT	1	>1
Patients with 1st LVV given after OLT	45 (77.5)	13 (22.4)
VZV vaccine, N (%)	41 (77.4)	12 (22.6)
MMR vaccine, N (%)	44 (77.2)	13 (22.8)
Patients re-vaccinated after OLT	29 (76.3)	9 (23.7)
VZV vaccine, N (%)	29 (76.3)	9 (23.7)
MMR vaccine, N (%)	25 (78.1)	7 (21.9)
Patients who did not receive LVV after OLT	89 (62.7)	53 (37.3)

Table 4. Tacrolimus Levels at 2-year Follow Up

Patient Group	Tacrolimus Level (ng/mL) Mean (SD)
Patients with 1st LVV given after OLT	4.8 (1.8)
VZV vaccine	4.9 (1.7)
MMR vaccine	4.8 (1.8)
Patients re-vaccinated after OLT	6.3 (3.1)
VZV vaccine	6.3 (3.1)
MMR vaccine	6.2 (2.9)
Patients with no LVV after OLT	5.7 (2.3)

Comparison of immunosuppressive regimens for those receiving their first LVV following OLT, those re-vaccinated with any LVV following OLT and those receiving no LVV following OLT

Results

- Children who received their first LVV following OLT were significantly younger than those who were re-vaccinated post-OLT (median 0.78 vs 2.44 years, p = 0.00)
- LVV was given sooner following transplant among children who received their first LVV post-OLT than in those who were revaccinated (median 649 [range: 134-3957] vs. 907 [range: 206-3430], p = .007)
- Children who received LVV following OLT were more often receiving single agent IS compared to children who were not vaccinated: 77.1% vs 62.7% p = 0.019
- There were no significant differences in tacrolimus levels at 2 years among patients who received first LVV, were re-vaccinated, or were not vaccinated post-OLT.
- There were a number of patients at both centers on more than one IS agent received LVV, and no AEs were observed in this group

Limitations

- As a retrospective study, only immunizations documented within the EMR were captured
- Similarly, only adverse events significant enough to be reported and documented in the EMR were captured
- VZV and MMR serologies were not routinely checked in those who received LVV post-OLT, so serologic efficacy could not be determined from this study

Conclusions

- Within this cohort of pediatric patients, LVV following OLT was safe and well tolerated, with limited adverse events associated with administration and no documented episodes of vaccine-type virus reactivation
- Children who received their first LVV following OLT were significantly younger at transplant than those who were re-vaccinated post-OLT; this likely relates to their young age at transplant, prior to safely receiving LVV series
- A subset of patients who appeared to qualify for LVV based on local guidelines did not receive LVV, suggesting missed opportunities continue to be identified for providing protection in this population
- There were no documented cases of MMR or VZV during the two year follow up period of those vaccinated