Efficacy and safety of measles, mumps, rubella and varicella live viral vaccines in transplant recipients receiving immunosuppressive drugs

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Background: **This review was designed to summarize published data on the efficacy and safety of live viral vaccines for measles, mumps, rubella, or varicella in post-transplant patients currently on immunosuppression.**

Data sources: **Medline, EMBASE and Evidence Based Medicine Reviews were searched from 1966 to November 2007 for case reports or studies describing the efficacy and/or safety of live attenuated measles, mumps, rubella, or varicella vaccine in children on immunosuppression following solid organ, bone marrow or stem cell transplantation.**

Results: **The review identified 6 case series and 2 case reports describing 114 solid organ transplant recipients and one case series describing 27 bone marrow transplant recipients who had received a combined total of 206 doses of live varicella, measles, mumps, or rubella vaccine while on immunosuppression. Post-immunization titers were in the immune range in 109 of the 171 situations where they were measured following a single dose of vaccine (64%) and in 15 of 22 situations following 2 doses (68%). There were no major safety concerns in this small sample.**

Conclusion: **There are insufficient published data to derive evidence-based guidelines for use of live viral vaccines in transplant recipients on immunosuppression but preliminary data on efficacy and safety suggest that the use of these live viral vaccines in transplant recipients still on immunosuppression could be a reasonable strategy.**

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Key words: **measles vaccine; transplantation; vaccination; varicella vaccine**

Introduction

Primary prevention of potentially serious viral infections is vital in transplant recipients as compared with normal hosts, and they have impaired clinical signs and symptoms of disease, more rapid progression of disease, and increased susceptibility to severe disease. Immunization prior to transplantation is not always practical. Secondary vaccine failure can occur in marrow or stem cell recipients due to marrow ablation. Therefore, immunization post-transplant may be necessary, but is complicated by the fact that response to vaccines can be impaired by immunosuppression and that live vaccines are not licensed for use in this population because of the increased risk of clinical disease from the vaccine strain of the virus.

The purpose of this review was to summarize available data on the efficacy and safety of live viral vaccines for measles, mumps, rubella, or varicella in post-transplant patients currently on immunosuppression.

Methods

Medline, EMBASE and Evidence Based Medicine Reviews (including Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, and Cochrane Central Register of Controlled Trials) were searched from 1966 to November 2007 inclusive for case reports and studies describing the efficacy and/or safety of live attenuated measles, mumps, rubella, or varicella vaccine in children on immunosuppression following solid organ, bone marrow or stem cell transplantation. Key words

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including *Vaccines/Attenuated, Transplantation, Transplant, Immunosuppressed, Immunosuppression, Immunization, Immunizations, MMR, Measles, Measle, Mumps, Mump, Rubella, Vaccines, Vaccine, Passive Immunization, Active Immunization, Measles Virus, Measles Vaccine, Measles Mumps Rubella Vaccine, Measles Rubella Vaccine, Measles Antibody, Vaccination Reaction, Chickenpox, Varicella Vaccine, Chickenpox Vaccine* were searched in appropriate combinations and all papers related to immunization of transplant patients were assessed to look for case reports and studies that met the inclusion criteria. The reference lists of all these case reports and studies were hand searched, and the author's name was searched in the Web of Science search engine to determine if the paper had been cited in other original works.

Results

Six studies[1-6] and two case reports[7,8] met the inclusion criteria. They reported use of 179 doses of measles vaccine, measles, mumps, and rubella vaccine (MMR), and/or varicella vaccine in 112 children and 2 adults who had received solid organ transplants 1.5 to 201 months previously and were on a wide variety of immunosuppressive regimes (Table 1). Post-immunization titers were in the immune range in 82 of the 145 situations where they were measured following a single dose of vaccine (57%), in 15 of 22 situations following 2 doses (68%), and in 2 of 2 cases following 3 doses with results being similar for MMR and varicella vaccines (serology only measured in 2 of the 3 cases) (Table 2). Waning of titers occurred in all studies that included follow-up serology.[1-3]

Ten of the 89 patients who received varicella vaccine developed possible vaccine-associated localized or generalized rash[2,3,5-8] although isolation of virus was attempted in only one case, yielding the vaccine strain.[8] The duration of clinical follow-up was not always reported, but 3 cases of mild varicella[2] and no cases of measles, mumps, or rubella occurred in vaccine recipients.

Only one study evaluated use of live viral vaccines in post-bone marrow transplant (BMT) patients on immunosuppressive therapy, with MMR being given to 27 patients 9 to 18 months post-transplant.[9] All had immune titers for measles post-immunization (although only 7 had non-immune titers pre-immunization) and there were no moderate or severe vaccine-related adverse reactions. The authors documented one patient with low grade fever (<38.5ºC) and 5 patients with myalgias in 51 BMT patients immunized, but did not outline which of these adverse events occurred in the 27 patients still on immunosuppression. None of the patients had vaccine-related rashes.

Discussion

There is a paucity of data on the efficacy or safety of administration of live viral vaccines to transplant patients on immunosuppression. With regard to short-term efficacy, about two-thirds of patients who had been immunized against measles, mumps, rubella, or varicella were seropositive in post-immunization serology. The first limitation of these data on short-term efficacy is that only one study included a control group,[3] so the expected seroconversion rate is not known. The second limitation is that pre-immunization seronegativity was not documented in most studies, so one cannot be certain the immune titers always occurred from the administered vaccine rather than from previous immunization or natural infection. In fact, in the BMT study, the vast majority of children were sero-positive for measles prior to immunization. The third limitation is that protective titers are not consistently well-validated for the multitude of assays employed in the various studies. In particular, laboratory assays designed to detect antibodies to varicella virus will not consistently detect vaccine strains, so it is possible that the true seroconversion rates for this virus are higher than those reported.

With regard to long-term vaccine efficacy, waning of titers to the seronegative range was more common than would be expected in the normal population in the study with the most extensive long-term follow-up,[2] but it is important to recognize that an unknown number of patients with seroreversion maintain cell-mediated immunity and will mount a protective booster response upon rechallenge with the virus. Furthermore, even in the normal host, it is now accepted that two doses of measles and varicella vaccine are ideal to confer a life-long immunity. Only one study reported results following the administration of more than one dose of vaccine[3] and only non-responders were given two or three doses. The efficacy of post-transplant immunization in preventing infection cannot be assessed from this review as the vast majority of patients were likely not exposed to the virus or they were immunized against during the study period. The occurrence of 3 cases of varicella in 37 immunized patients was not unexpected as the efficacy of varicella vaccine was <90% in the normal host.[10] The fact that the cases were mild suggests the vaccine has some efficacy despite not preventing disease.

Even if vaccination is efficacious, the primary reason for avoiding live viral vaccines in transplant recipients

Table 1. Efficacy and safety of live attenuated measles, mumps, rubella and varicella vaccine in solid organ transplant recipients (all received a single dose unless otherwise noted).

Author Year	Organ	Age at immunization	Vaccine type	Time to immunization post-transplant	Immunosuppression at time of immunization	Method of measuring IgG titers and titer considered to be immune	Number with immune titers post-immunization	Number with immune titers at follow-up	Clinical follow-up
Rand 1993[1]	Orthotopic liver (all <3 years old) (*n*=18)	16-73 mon (mean 34 mon)	MMR (*n*=6) or measles (*n*=12)	1.5-65 mon (mean 23 mon)	CsA+Pred (*n*=13) CsA+Pred+AZA (*n*=4) TAC (*n*=1) OKT3+CsA+ Pred (*n*=1)	Solid phase fluorescent immunoassay >12 (8-12 indeterminate)	7/17 (41%) with 3/17 (18%) indeterminate and 1/17 NR*	Seroreversion occurred in the only case with follow-up titers	1 episode of acute rejection 3 weeks after vaccine No documented measles exposure or disease
Zamora 1994[2]	Renal (*n*=17)	4.4-18.4 y (mean 11.6 y)	Varicella†	3-124 mon (mean 52 mon)	Pred, CsA+AZA with lymphocyte count >1500/mm^3	ELISA >1:40	11/17 (65%)	At 3-6 mon 14/17 (82%); At 12 mon 16/17 (94%); At 24 mon 13/17 (76%); At 36 mon 9/17 (53%); At 48 mon 6/17 (35%)	1 case of mild VZV infection 15 days post-vaccine† 3 cases of mild VZV infection 2-4 years post-vaccine‡
Kano 2002[3]	Living-related donor liver (*n*=13)	NR	MMR and varicella§	>12 mon	FK506+CsA with low blood levels and no corticosteroids in previous 6 months	ELISA for rubella and mumps ≥2.0 units HI for measles ≥1:8	Measles 11/13 (85%); Mumps 6/6 (100%); Rubella 2/2 (100%); Varicella 5/7 (71%)	At 6-78 months, 8/13 for measles (64%), 100% for mumps (*n*=2) and rubella (*n*=6), 4/7 (57%) for varicella‖	No vaccine-related adverse events
Levitsky 2002[7]	Orthotopic liver (*n*=1)	60 y	Varicella¶	11 mon	TAC, Sirolimus+Pred	NR	NR	NR	Rash 3 weeks post-vaccine resolved with 5 days oral acyclovir and recurred 2 days later with antigen detection test positive for VZV, resolved with IV acyclovir‡
Chaves 2005[4]	Renal (*n*=6)	11-17 y	Varicella**	12-91 mon	MMF+Pred+CsA (*n*=3) MMF+Pred+Tac (*n*=2) AZA+Pred+TAC (*n*=1)	Immunosorbent assay using an in-house assay >500 mAU/mL (100-499 indeterminate)	4/6 (66.6%) 6-8 weeks after vaccine with 1/6 (17%) indetereminate	NR	No vaccine-related adverse events Follow-up for 8 weeks only
Weinberg 2006[5]	Liver (*n*=14), small bowel (*n*=1) and combined (*n*=1)	8-68 mon (median 13 mon)	Varicella¶	8-67 mon	Pred (*n*=9) CsA (*n*=1) TAC (*n*=14) Sirolimus (*n*=1)	Commercial EIA kit (Diamedix) >20 mIU/ml††	13/15 (87%) ≥12 weeks post-vaccine	NR	5 injection site reactions 4 fevers 1-27 days post-vaccine 4 rashes 1-24 days post-vaccine, of which 3 were treated with acyclovir no rejection in the 6 weeks post-vaccine no proven varicella with 4 children having exposures, but one treated with acyclovir as liver enzymes increased
Khan 2006[6]	Liver (*n*=31)	12-218 mon (median 36 mon)	MMR‡‡	4-201 mon (median 26 mon)	CsA or TAC	Not standardized	19/26 (73%)	NR	NR
Khan 2006[6]	Liver (*n*=35)	12-180 mon (median 46 mon)	Varicella§,‡‡	4-173 mon (median 39 mon)	CsA or TAC	Not standardized	20/31 (65%)	NR	3 injection site vesicular rashes with tactile fever reported by parents
Kraft 2006[8]	Cardiac (*n*=1)	36 y	Varicella¶	2 y	CSA+MMF	NR	NR	NR	Rash on day 27 confirmed to be vaccine strain of VZ treated orally initially but then admitted for IV acyclovir

*: Titers were not measured in one patient. All titers were immune if measured <2 months after immunization. †: OKA strain. ‡: Varicella virus typing results not reported to determine if this was a vaccine or wild-type. §: Varicella vaccine strain not reported. ‖: Thirty-five patients aged 1-15 years with allergic diseases and no liver pathology were reported as controls. Their seroconversion data is not provided but the discussion states they retained varicella antibodies for 3 years. ¶: VARIVAX®, Merck&Co Inc. **: Varilrix® SmithKline Beecham Biologicals. ††: Also performed lymphocyte proliferation assay with 12/14 being positive ≥12 weeks post-vaccine. ‡‡: Total of 42 children received a vaccine with 7 receiving MMR, 11 receiving varicella vaccine, and 24 receiving both. Thirteen of these children received one dose of MMR, 15 received 2 doses MMR, and 3 received 3 doses MMR. Seven children received two doses of varicella vaccine. AZA: azathioprine; CsA: cyclosporine; ELISA: enzyme-linked immunoabsorbent assay; HI: hemagglutinin inhibition; IgG: immunoglobulin G; MP: methylprednisolone; MMF: mycophenolate; MMR: measles, mumps, and rubella vaccine; NR: not reported; Pred: prednisone; TAC: tacrolimus; VZV: varicella zoster virus.

Table 2. Efficacy of different live viral vaccines in the patients who had received a solid organ or bone marrow transplant

Vaccine	Number of patients	Number with immune titers post-immunization
Monovalent measles	12	5/11 (45%) immune and 1/11 (9%) IND
MMR	59 (1 dose), 15 (2 doses), and 3 (3 doses)	Measles: a) 1 dose 49/76 (64%) immune*, 1/76 (1%) IND b) 2 doses 9/15 (60%) immune† c) 3 doses 2/2 (100%) immune Mumps: 6/6 immune Rubella: 2/2 immune
Varicella	82 (1 dose) and 7 (2 doses)	a) 1 dose 47/76 (62%) immune and 1/76 (1%) IND‡ b) 2 doses 6/7 (86%) immune

*: including 18 children who had repeat doses as they did not seroconvert following the first dose. †: including 3 children who had repeat doses as they did not seroconvert following two doses; ‡: including 7 children who had a repeat dose as they did not seroconvert following the first dose. IND: indeterminate; MMR: measles, mumps, and rubella vaccine.

has been safety concerns. The only possible vaccine-related adverse events in this review of 179 doses of live viral vaccines included 1 case of rejection 3 weeks post-immunization[1] and 9 cases of possible and 1 case of proven vaccine-associated varicella in 89 patients given 96 doses of varicella vaccine.[2-8] However, surveillance for adverse events was passive in most studies so serious events could have been missed. Vaccine-associated varicella occurs in about 10% of normal hosts[11] so the number of cases in this study is not unexpected. The rash can be localized or generalized and classically results in mild disease with no complications.[11] Two of the cases of vaccine-associated varicella in the current study required hospitalization because the rash continued to spread[8] or recurred[7] rather than because there was evidence of dissemination.

Even if vaccines are efficacious and serious vaccine-associated adverse events are rare, one would only choose to use live viral vaccines in transplant recipients if the diseases they prevent are likely to result in significant morbidity. Although endemic measles does not occur in most developed countries, the non-immune transplant recipients who travel to endemic areas may be at risk being exposed to imported cases. Immunocompromised hosts with measles may not develop the characteristic rash so the diagnosis is often delayed. The case fatality rate is increased in this population, and there is still no licensed effective anti-viral therapy. With regard to varicella, infection occurred in 18% of pediatric renal transplant recipients at <2 years of age and in 13% of 2 to 5-year-old recipients and resulted in death of a school-aged child 17 months post-transplant.[12] Multiple centers have reported severe varicella infections in solid organ transplant recipients despite appropriate use of acyclovir and immunoglobulin.[13] Mumps and rubella infection are of lesser concern than are measles and varicella infection as the severity of illness is not clearly increased in transplant recipients. Nonetheless, it is logical to administer MMR rather than monovalent measles vaccine as the incidence of vaccine-related adverse events is remarkably similar, and even in the normal host mumps encephalitis and congenital rubella syndrome can be life-altering events.

Conclusion

Live viral vaccines should generally be avoided in patients with bone marrow or stem cell transplants on immunosuppression as most of them will be off immunosuppression by 24 months post-transplant. The data in the literature are limited to administration of MMR to 27 patients.[9] During an outbreak, immunization prior to 24 months post-transplant may be advisable[9] but further data must be accumulated before this becomes a routine practice.

For solid organ transplant recipients, the most important strategy is to administer routine live viral vaccines prior to transplantation. It is recognized that the transplantation is relatively contra-indicated during the incubation period of the virus given in the vaccine as the attenuated strain could produce severe disease in the face of high-dose immunosuppression. Passive maternal antibodies interfere with seroconversion to live vaccines in young infants, but seroconversion as early as 6 months of age has been described. Therefore, some transplant centers administer live vaccines to potential solid organ recipients starting at 6 months of age, but the results of this strategy are yet to be reported. Following solid organ transplantation, antibody titers to measles, mumps, rubella and varicella should be measured at >12 months post-transplant, recognizing that patients who had immune titers pre-transplant sometimes serorevert.[14] Although a recent survey of 16 pediatric lung transplant centers in North America and Europe showed that none recommended immunization with live viral vaccines post-transplant

outside a research protocol,[15] this may indeed be a safe practice in some settings. The transplant centers that have administered live viral vaccines to transplant recipients on immunosuppression should report their results, and prospective studies of the efficacy and safety of this practice should be encouraged, recognizing that results may vary depending on the timing of administration of vaccine post-transplant and the immunosuppressive regimen that is prescribed.

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