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REVIEW

Live attenuated vaccines in patients receiving immunosuppressive agents

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Abstract

The use of live attenuated vaccines in patients with immunosuppressive agents is contraindicated in package inserts and guidelines in Japan and other countries. However, patients receiving immunosuppressants have a high risk of infectious disease becoming severe, and the necessity to prevent infectious disease is high. To date, 2,091 vaccinations have been reported in 25 reports of live attenuated vaccines in people receiving immunosuppressants. Twenty-three patients (1.1%) became infected with the virus strain used in the vaccine, which was varicella virus in 21 patients. No reports have described life-threatening complications. A prospective study at the National Center for Child Health and Development conducted under certain immunological conditions (CD4 cell count $\geq 500/mm^3$, stimulation index of lymphocyte blast transformation by phytohemagglutinin (PHA) ≥ 101.6, serum immunoglobulin G ≥ 300 mg/dL) confirmed the serological effectiveness and safety. The evidence suggests that live attenuated vaccines can be used even in combination with immunosuppressants. Further evidence must be gathered and immunological criteria investigated to determine the conditions for safe use. Depending on the results of these investigations, the wording in package inserts and guidelines may need to be revised.

Keywords Immunosuppressive agent · Steroid · Live attenuated vaccine · Contraindication · Cellular immunodeficiency · Infectious disease · Varicella

Introduction

In package inserts and various guidelines in both Japan and other countries, the use of live attenuated vaccines in patients with immunosuppressive agents is clearly contraindicated. However, as patients receiving immunosuppressants are at elevated risk of severe infectious disease, they need to prevent infectious disease more than healthy individuals. In current society, many clinicians struggle with the dilemma of the necessity of prevention of infection and being unable to vaccinate immunosuppressed individuals against measles and varicella. Discontinuing lifelong immunosuppressants is difficult in many patients after solid organ transplants or other conditions, and under current conditions these patients can never be vaccinated with live attenuated vaccines. This article presents an overview of the current state of evidence regarding live attenuated vaccination of patients receiving immunosuppressants, vaccination reports to date, problems faced in performing vaccinations, and the future outlook.

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Infectious diseases for which live attenuated vaccines are needed for prevention

Infectious diseases for which live attenuated vaccines are needed for prevention include measles, rubella, varicella, mumps, rotavirus, yellow fever, and tuberculosis. The vaccination rate for the measles-rubella (MR) vaccine is very good in Japan, with more than 95% of the general population having completed the vaccination by 2 years old. Reports of measles patients have decreased with the rise in the vaccination rate in Japan, which was certified by the World Health Organization in 2015 as a country that has eliminated measles. However, reports of measles have not completely ceased, as imported cases are still encountered along with occasional epidemics. Major epidemics of rubella are also occasionally seen, and in epidemic years many reports describe patients with congenital rubella syndrome. In Japan, varicella became a target disease for routine

vaccination in November 2014. Since then, the vaccination rate has risen each year, and currently more than about 95% of children have received at least one dose by age 2. Accordingly, the number of infections has decreased in recent years. Even so, epidemics of varicella are still sometimes seen. The mumps vaccine remains a voluntary vaccination and infections are frequently seen. Particularly when the disease is contracted in adults, problems such as orchitis in men are described.

Although the number of patients infected with measles, rubella, varicella, and mumps are tending to decrease compared to the past, epidemics sometimes occur even today. Patients receiving immunosuppressants who cannot be administered live attenuated vaccines are thus exposed to the risk of these infectious diseases.

Current status of live attenuated vaccines in people receiving immunosuppressants or steroids

The current status of live attenuated vaccines in people receiving immunosuppressants or steroids is summarized in Table 1. The package inserts and several guidelines in Japan and the United States show that live attenuated vaccines are generally contraindicated in patients with immunosuppressive agents, although varicella vaccine is relatively accepted if the immunosuppression is mild, as it was originally developed for immunocompromised individuals. The American Academy of Pediatrics' Red Book 2021–2024, Infectious Diseases Society of America 2013 [1], Advisory Committee on Immunization Practices, and others also state that the use of live attenuated vaccines is contraindicated in patients receiving immunosuppressants.

Reasons for contraindicating live attenuated vaccines in patients receiving immunosuppressants

In patients with a highly suppressed immune status (particularly cellular immunodeficiency), development of fatal viral infections from the vaccine strain in the live attenuated vaccine is a known possibility. This includes miliary tuberculosis after BCG vaccination, life-threatening measles infection after measles vaccination, disseminated varicella after varicella vaccination, meningoencephalitis after mumps vaccination, paralysis after live polio vaccination, and intractable diarrhea after rotavirus vaccination. Live attenuated vaccines therefore cannot be used in patients with cellular immunodeficiency.

For reference, live attenuated vaccines are contraindicated for individuals with cellular and humoral immunodeficiency, such as severe combined immunodeficiency, Wiskott–Aldrich syndrome, and hyper-immunoglobulin (Ig)M syndromes, and humoral immunodeficiency such as X-linked agammaglobulinemia, but live attenuated vaccines except for BCG can be used for individuals with diseases that cause abnormalities in phagocytes (neutrophils, monocytes, macrophages), such as chronic granulomatous disease and congenital neutropenia. These vaccines can also be used in patients with disorders such as ataxia-telangiectasia, selective IgA deficiency, and complement deficiency. We should therefore be aware that it is not the case that live attenuated vaccines cannot be used in all immunodeficiencies, but they definitively cannot be used in patients with cellular immunodeficiencies and humoral immunodeficiencies.

Secondary infections from the vaccine strains have also been reported with varicella vaccines, mumps vaccines, rotavirus vaccines, live polio vaccines, and others. The incidences of varicella rash (or herpes zoster) from the vaccine strain after varicella vaccination and parotid swelling after mumps vaccination are very low, but cases have been reported even in previously healthy individuals, and multiple case reports have described secondary infections in siblings and others. However, since the viruses involved are attenuated, the disease does not become severe unless the individual is in an immunocompromised state. The rotavirus vaccine and live polio vaccine are known to be excreted in feces for a short time after inoculation in infants, and so should not be used if there is an immunocompromised person in the family. Inactivated polio vaccines have now been introduced in Japan and live vaccines are no longer used.

Given the above, live attenuated vaccines are indisputably contraindicated for individuals in a highly immunosuppressed state, particularly those with cellular immunodeficiency. Accordingly, package inserts for immunosuppressants contraindicate concurrent use with live attenuated vaccines. However, not all patients who are receiving immunosuppressants develop cellular immunodeficiency. Rather, the parameters of cellular immunity on blood tests are often mostly normal.

Risk of severe infection in patients receiving immunosuppressants

A large number of reports have described death from varicella in patients undergoing immunosuppressive therapy or immunocompromised patients (Table 2) [2–14]. Varicella is known to cause internal organ damage in an immunosuppressed state, and is sometimes complicated by multiple-organ failure. Our Center has also experienced a patient with multiple-organ failure from varicella who could not be saved. Depending on the report, the mortality rate is within a wide range of 0–80%. However, looking at the total for

Table 1 Current status of live attenuated vaccines in people receiving immunosuppressants or steroids

	Live vaccines under immunosuppressants (except for varicella vaccines)	Varicella vaccines under immunosuppressants	Live vaccines under steroid (except for varicella vaccines)	Varicella vaccines under steroid
Package inserts of immunosuppressants in Japan	Contraindicated	Not stated		
Package inserts of prednisolone in Japan			Should not be given in high dose [a)]	Not stated
Package inserts of methylprednisolone in Japan			Contraindicated	Not stated
Package inserts of live vaccines in Japan	Contraindicated		Contraindicated	
Package inserts of varicella vaccines in Japan		Not stated		Can be used if cellular immunity is normal
Package inserts of MMR in the United States	Contraindicated		Should not be given in high dose [a)]	
Package inserts of varicella vaccines in the United States		Contraindicated		Should not be given in high dose [a)]
Vaccination Guidelines in Japan (Public Foundation of Vaccination Research Center)	Should not be given	Should not be given	Should not be given in high dose [a)]	
2008 Hematopoietic Cell Transplantation Guidelines in Japan	Contraindicated	Contraindicated	Should not be given	Should not be given
2014 Vaccination Guidelines for Organ Transplant and Immunocompromised Children in Japan	May be considered as clinical research	May be considered as clinical research	May be considered as clinical research	May be considered as clinical research
2018 Adult Organ Transplant Patient Vaccination Guidelines in Japan	May be considered as clinical research	May be considered as clinical research	May be considered as clinical research	May be considered as clinical research
American Academy of Pediatrics' Red Book 2021–2024	Contraindicated	Can be used under low dose	Should not be given in high dose [a)]	Should not be given in high dose [a)]
Infectious Diseases Society of America 2013	Contraindicated	Can be used under low dose	Should not be given in high dose [a)]	Should not be given in high dose [a)]
Advisory Committee on Immunization Practices	Contraindicated	Can be used under low dose	Should not be given in high dose [a)]	Should not be given in high dose [a)]

MMR, measles, mumps and rubella combined vaccine

[a]High dose of steroid is defined as prednisolone of ≥ 2 mg/kg or ≥ 20 mg if the patient is 10 kg or more

reports presented in this document, 23 deaths were identified among a total of 326 patients (mortality rate, 7.1%). This is very high compared with the 0.002–0.004% reported among healthy individuals. For measles, we were unable to find any case series with large numbers of patients receiving immunosuppressants, but the mortality rate from measles among immunocompromised patients is very high, at 20.0–83.3% [15–19], and all cases showed complicating pneumonia or encephalitis (mortality rate in healthy individuals, 0.1–0.3%). For mumps, reports have included death from meningoencephalitis in a patient with combined immunodeficiency after bone marrow transplantation [20]. Our responsibility is to protect children for whom there is no option but to receive immunosuppressants over the long term from these viral infections.

For patients with pre-existing conditions, the fact that contracting an infection can cause recurrence or exacerbation of the primary disease is also problematic. Infections triggering a recurrence of nephrotic syndrome, exacerbation of rheumatic diseases such as systemic lupus erythematosus, acute rejection following kidney transplants, or other problems, are not rare. Incidentally, two mechanisms are thought

Table 2 Reports on varicella in patients receiving immunosuppressants [2–14]

Reference	Subjects	Children/Adults	Patients	Deaths	Mortality rate (%)
2	Kidney transplant recipients	children	8	2	25.0
3	Unvaccinated kidney transplant recipients	children	22	3	13.6
4	Kidney transplant recipients	children	19	1	5.3
5	Kidney transplant recipients	children	66	1	1.5
6	Kidney transplant recipients	children	44	0	0.0
7	Liver transplant recipients	children	14	2	14.3
8	Liver transplant recipients	children	22	0	0.0
9	Heart transplant recipients	children	14	0	0.0
10	Immunocompromised patients	children	31	4	12.9
11	Malignant tumor patients	children	77	4	5.2
12	Kidney transplant recipients	adults	5	4	80.0
13	Kidney transplant recipients	adults	4	2	50.0
14	Healthy people	adults/children			0.002–0.004

to be involved in these "recurrences" or "exacerbations" of primary disease triggered by infection: from immunological stimulation within the body from the infection, and from temporarily decreased doses or discontinuation of immunosuppressants following the development of an infection.

Reasons why the use of live attenuated vaccines is permanently difficult in patients receiving immunosuppressants

Steroid-resistant nephrotic syndrome and frequently relapsing nephrotic syndrome, both of which require the continuation of immunosuppressants, account for about 40% of all nephrotic syndromes and often occur at relatively young ages. These pathologies are also frequently experienced by patients who have not been vaccinated with live vaccines such as the combined measles-rubella vaccine or varicella vaccine. In nephrotic syndrome patients, repeated recurrence is common when immunosuppressants such as cyclosporine, MMF, and mizoribine are tapered or discontinued. Even if an immunosuppressant can be discontinued in these patients, live attenuated vaccines can no longer be used due to recurrence. Among recipients of solid organ transplants, all those in whom vaccination is possible are vaccinated before the transplant with a live vaccine, and transplantation is then performed after confirming a rise in antibodies. However, some cases cannot be administered a live attenuated vaccine in time, such as in liver transplants for fulminant liver failure during infancy. After the transplant, immunosuppressant therapy is continued for life, so live attenuated vaccines can never be used in the lifetime of that patient. Meanwhile, by continuing immunosuppressive therapy, it is not uncommon for antibodies to subsequently disappear, exposing the patient to a risk of viral infection.

To protect patients in whom discontinuation of such immunosuppressants is difficult from infection, the use of live attenuated vaccines is considered preferable during the time when the disease condition is stable under immunosuppressants. In fact, even when a patient is receiving immunosuppressants, a fair number of clinicians administer live attenuated vaccines after fully explaining to the family and patient that such use is technically contraindicated.

Reports in the literature on the use of live attenuated vaccines in patients receiving immunosuppressants

We identified 25 reports, including clinical research, case series, and case studies, on the use of live vaccines in patients receiving immunosuppressants [21–45]. Many of the patients involved had undergone solid organ transplants, and a large proportion were children (Table 3). A total of 2,091 vaccinations were administered (measles, n = 123; rubella, n = 82; varicella, n = 858; mumps, n = 418; yellow fever, n = 21; MR, n = 344; MMR, n = 244; measles-mumps-rubella-varicella (MMRV), n = 1) (Table 4). Adverse events were the development of vaccine-strain viral infections in 23 patients (1.1%). This included varicella rash after varicella vaccination or MMRV vaccination in 21 of 859 patients (2.4%), and parotid swelling after mumps in 2 of 418 mumps vaccination (2 of 663 vaccinations of mumps, MMR, or MMRV, 0.3%). The risk of vaccine-strain viral infections may be higher than in healthy individuals, but since the vaccines are attenuated, the infections seem milder than those from wild strains, and no life-threatening complications have been seen. Notably, nearly all viral infections from the vaccine strain have involved varicella, and not a single case of measles or rubella has been reported.

Table 3 Previous reports on live vaccines in patients receiving immunosuppressants [16–40]

Reference	Subjects	Vaccine	Vaccination conditions	Seroconversion rate	Adverse events
21	Post-liver transplant (n = 18) Age: 16–73 mo (Pediatric patients)	MMR (n = 6) Measles (n = 12)	≥ 6 mo after liver transplant without rejection	Measles 7/17 (41%)	Chronic rejection (n = 1)
22	Post-kidney transplant (n = 17) Age: 4.4–18.4 yo (Pediatric patients)	Varicella (n = 17)	Lymphocyte count > 1500/mm^3	Varicella 11/17 (65%)	Varicella rash (n = 3)
23	Post-liver transplant (n = 13) Age: Not given (Pediatric patients)	Measles (n = 13) Rubella (n = 2) Varicella (n = 7) Mumps (n = 6)	1. ≥ 6 mo after discontinuation of steroids 2. Tacrolimus trough < 5 ng/mL 3. Cyclosporine trough < 50 ng/mL 4. ≥ 1 year after liver transplant 5. Normal liver function 6. No acute rejection for ≥ 6 mo	Measles 11/13 (85%) Rubella 2/2 (100%) Varicella 5/7 (71%) Mumps 6/6 (100%)	None
24	Post-liver transplant 60 yo woman (n = 1)	Varicella (n = 1)	Not given	Not given	Appearance of varicella rash after 3 weeks. Acyclovir administered. Presumed to be varicella from vaccine strain
25	Post-kidney transplant (n = 6) Age: 11–17 yo (Pediatric patients)	Varicella (n = 6)	1. ≥ 6 mo after kidney transplant 2. No repeat infection 3. Stable kidney function	Varicella 4/6 (67%)	None
26	Post-liver transplant (n = 14) Post-small bowel transplant (n = 1) Post-liver, small bowel transplant (n = 1) Age: 8–68 mo (Pediatric patients)	Varicella (n = 16)	1. ≥ 12 mo after birth 2. ≥ 6 mo after liver transplant 3. ≥ 12 mo after small bowel transplant 4. No acute rejection for ≥ 1 mo	Varicella 13/15 (87%)	Local reaction at injection site (n = 5) Temporary fever (n = 4) Varicella rash (n = 4)
27	Post-liver transplant (n = 42) Age: 12–218 mo (Pediatric patients)	MMR (n = 31) Varicella (n = 35)	1. Tacrolimus trough 3–10 ng/mL 2. Cyclosporine trough 30–120 ng/mL	Measles 19/26 (73%) Varicella 20/31 (65%)	Varicella rash at injection site (n = 3)
28	Post-heart transplant 36 yo man (n = 1)	Varicella (n = 1)	Not given	Not given	Appearance of varicella rash after 24 h. Treated with famciclovir. Definitive diagnosis as vaccine strain with PCR
29	Inflammatory bowel disease (n = 4) Age: 6 yo, 14 yo, 15 yo, 20 yo (6 patients reported, but among these, only 4 patients received 6MP)	Varicella (n = 4)	Not given	Varicella 3/4 (75%)	None
31	Post-kidney transplant (n = 14) Post-heart transplant (n = 3) Post-liver transplant (n = 2) Age: 11–69 yo (Pediatric/adult patients)	Yellow fever (n = 19)	Not given	Not given	Local reaction (n = 1)

Table 3 (continued)

Reference	Subjects	Vaccine	Vaccination conditions	Seroconversion rate	Adverse events
32	Post-kidney transplant 55 yo man (n = 1)	Yellow fever (n = 1)	Not given	Acquisition of yellow fever antibodies after vaccination	Elevated AST, ALT were seen; Intravenous immunoglobulin was administered
33	Post-liver transplant (n = 39) Age: 12–180 mo (Pediatric patients)	Measles (n = 34) Rubella (n = 31) Varicella (n = 33) Mumps (n = 33)	1. ≥ 1 y after liver transplant 2. ≥ 6 mo after discontinuation of steroids 3. Tacrolimus trough < 5 ng/mL	After first dose Measles 11/25 (44%) Rubella 19/27 (70%) Varicella 6/19 (32%) Mumps 12/25 (48%)	No serious events
34, 35	Post-liver transplant (n = 48) Age: 3–18 yo (Pediatric patients)	Measles (n = 48) Rubella (n = 35) Varicella (n = 55) Mumps (n = 58)	1. ≥ 2 y after liver transplant 2. Normal liver function 3. No acute rejection for ≥ 6 mo 4. Prednisolone < 0.2 mg/kg 5. Tacrolimus trough < 5 ng/mL 6. Cyclosporine trough < 100 ng/mL Infants 1. Lymphocyte count > 1500/mm^3 2. CD4 + cell count > 700/mm^3 Children 1. Lymphocyte count > 1000/mm^3 2. CD4 + cell count > 500/mm^3 3. Normal lymphocyte blast transformation by PHA 4. Serum IgG > 500 mg/dL	After first dose Measles 36/36 (100%) Rubella 35/35 (100%) Varicella 23/33 (70%) Mumps 24/35 (69%)	Temporary fever (n = 2) Varicella rash (n = 1) Parotid swelling (n = 2)
36	Nephrotic syndrome (n = 60) Age: 1–25 yo (Pediatric patients, some adults)	MR (n = 33) Measles (n = 2) Varicella (n = 57) Mumps (n = 24)	1. CD4 + T-cell count ≥ 500/mm^3 2. PHA stimulation index ≥ 101.6 3. Serum IgG ≥ 300 mg/dL 4. If patient has history of using rituximab, B-cells have to be recovered 5. Prednisolone use none, < 1 mg/kg/day, or < 2 mg/kg every other day 6. Tacrolimus trough < 10 ng/mL or cyclosporine trough < 100 ng/mL 7. No recurrence for ≥ 6 mo	After first dose Measles 22/23 (95.7%) Rubella 19/19 (100%) Varicella 26/42 (61.9%) Mumps 8/20 (40.0%)	No serious events No infections originating from vaccine strain
30, 37	Post-liver transplant (n = 49) Age: Median 4 yo (Interquartile range, 2.7–6.8) (Pediatric patients)	Varicella 1st: 6 pts 2nd: 30 pts 3rd: 13 pts → total 135 immunizations	1. ≥ 1 y after liver transplant 2. No acute rejection for ≥ 2 mo 3. Tacrolimus < 0.3 mg/kg (trough < 8 ng/mL) 4. Lymphocyte count ≥ 750/mm^3	After 1–2 doses, seroconversion in all 49 people	Rubor around injection site in 5 patients Appearance of varicella in 4 patients (→ possibility of varicella from vaccination)
38	Post-liver transplant (n = 44) (Pediatric patients)	MMR (n = 70)	Not given	After first dose Measles 39/40 (98%)	No serious events

Table 3 (continued)

Reference	Subjects	Vaccine	Vaccination conditions	Seroconversion rate	Adverse events
39	Post-kidney transplant 49 yo woman (n = 1)	Varicella (n = 1)	Not given	Not given	Appearance of varicella rash after 3 weeks. Acyclovir administered. Vaccine strain (Oka strain) verified with plasma PCR
40	Post-kidney transplant 50 yo man (n = 1)	Yellow fever (n = 1)	Not given	Not given	Developed wild-type yellow fever right after vaccination. Afterward, antibody-mediated rejection occurred
41	Post-kidney transplant 4 yo boy (n = 1)	MMRV (n = 1)	Not given	Not given	Varicella rash 5 weeks after vaccination
42	Inflammatory bowel disease, rheumatic disease, post-kidney and liver transplant, post-liver transplant, etc. (n = 32) Age: 1–25 yo (Pediatric patients, some adults)	MR (n = 22) Varicella (n = 28) Mumps (n = 14)	1. CD4 + T-cell count ≥ 500/mm^3 2. PHA stimulation index ≥ 101.6 3. Serum IgG ≥ 300 mg/dL 4. Prednisolone use none, < 1 mg/kg/day, or < 2 mg/kg every other day 5. Tacrolimus trough < 10 ng/mL or cyclosporine trough < 100 ng/mL	After first dose Measles 8/10 (80.0%) Rubella 15/15 (100%) Varicella 13/22 (59.1%) Mumps 9/13 (69.2%)	No fatal events. Varicella from vaccine strain in 1 person
43	209 post-liver transplant pediatric patients	MR (n = 225) Varicella (n = 224) Mumps (n = 215)	1. ≥ 2 y after liver transplant 2. Transplanted liver in good condition 3. Immunosuppressant was a single calcineurin inhibitor 4. Tacrolimus trough < 5 ng/ml or cyclosporine trough < 50 ng/ml 5. Several months lapsed since discontinuation of MMF or steroids	Not given	Vaccine-related side effects: fever, rash, etc. in 9 patients No verified viral infections from vaccine strain
44	781 vaccinations with live vaccines in patients receiving immunosuppressants or biologicals nationwide from 2013–2017	MR (n = 250) Measles (n = 16) Rubella (n = 14) Varicella (n = 287) Mumps (n = 214)	Not given	Not given	Development of varicella from vaccine strain in 2 people 29 cases of other non-specific adverse events, such as fever or rash
	Of the above, patients overlapping with the reports of Kamei 2018, Kamei 2020, Funaki 2020, patients taking single biological agents, and patients taking single steroids were excluded, leaving 286 vaccinations	MR (n = 84) Measles (n = 14) Rubella (n = 14) Varicella (n = 106) Mumps (n = 68)	Not given	Not given	Development of varicella from vaccine strain in 1 person 8 cases of other non-specific adverse events, such as fever or rash
45	97 post-liver transplant patients (2 were not taking immunosuppressant, so more accurately 95)	MMR (n = 137) Varicella (n = 132)	Not given	Not given	Fever in 2 people, injection site reaction in 2 people No vaccine strain viral infections

MR, measles and mumps combined vaccine; MMR, measles, mumps and rubella combined vaccine; MMRV, measles, mumps, rubella and varicella combined vaccine; MMF, mycophenolate mofetil; PHA, phytohemagglutinin; PCR, polymerase chain reaction, 6MP, 6 mercaptopurine

Table 4 Frequency of viral infections after live attenuated vaccines in patients receiving immunosuppressants [21–45]

Vaccine	Vaccinations	Vaccine-strain infections
Measles	123	0
Rubella	82	0
Varicella	858	20
Mumps	418	2
Yellow fever	21	0
MR	344	0
MMR	244	0
MMRV	1	1 (varicella rash)

MR, measles and mumps combined vaccine; MMR, measles, mumps and rubella combined vaccine; MMRV, measles, mumps, rubella and varicella combined vaccine

Table 5 Criteria for use of live attenuated vaccines in author's institution

1. Age ≥ 1 year old
2. Antibody titer (EIA-IgG) for one among measles, rubella, varicella, or mumps is negative (< 2.0) or (+) (2.0–4.0)
3. Immunological data satisfy the following:
   - CD4 cell count ≥ 500/mm^3
   - Stimulation index of lymphocyte blast transformation by PHA ≥ 101.6
   - Serum IgG ≥ 300 mg/dL
4. If a patient has a history of using rituximab, B-cells have to be recovered
5. If steroids are being administered, the following is satisfied: Prednisolone < 1 mg/kg/day or < 2 mg/kg every other day
6. Primary disease is stable for ≥ 6 months, no recurrence is seen
6. Discontinuation of immunosuppressant is difficult

Prospective study of live attenuated vaccines in nephrotic syndrome patients receiving immunosuppressants

Here we describe the "Prospective study of live attenuated vaccines for patients with nephrotic syndrome receiving immunosuppressive agents" conducted from May 2011 to March 2018 at the National Center for Child Health and Development [36]. In this study, live attenuated vaccines were administered to patients with antibody titers of < 4.0 enzyme immunoassay (EIA)-IgG against measles, rubella, varicella, mumps or other diseases, pre-vaccination peripheral blood CD4$^+$ T cells ≥ 500/mm^3, stimulation index of lymphocyte blast transformation by phytohemagglutinin (PHA) ≥ 101.6, and serum IgG ≥ 300 mg/dL (Table 5). We never administer vaccinations in patients who are under B-cell depletion after rituximab treatment, as influenza and COVID-19 vaccination are reported ineffective during this period in patients with lymphoma and rheumatic diseases [46–48]. Antibody titers (mean ± standard deviation (SD)) at 2 months after single doses were measles 36.7 ± 72.6, rubella 29.8 ± 23.3, varicella 8.9 ± 11.9, and mumps 3.5 ± 3.5. Seroconversion rates were 95.7% for measles (22/23 vaccinations), 100.0% for rubella (19/19 vaccinations), 61.9% for varicella (26/42 vaccinations), and 40.0% for mumps (8/20 vaccinations). Patients with positive conversion were followed. After 1 year, antibodies were relatively well maintained for measles (15/18 patients, 83.3%), rubella (16/17 patients, 94.1%), and varicella (23/30 patients, 76.7%), although antibodies for mumps tended to decrease (2/10 patients, 20.0%). Patients with antibodies (EIA-IgG) ≥ 10.0 at 2 months were confirmed to have maintained long-term immunity. Among vaccinated patients who displayed positive conversion of antibodies, not a single breakthrough infection was seen. Adverse events included recurrence of nephrotic syndrome in 2 patients and several events including fever and rash for which the relationship to the vaccine was unclear, but no serious adverse events. Not a single case of vaccine-strain viral infection was identified. If certain immunological conditions are met, live attenuated vaccines have been confirmed to be safe and effective even in patients with nephrotic syndrome receiving immunosuppressants.

Prospective study of live attenuated vaccines in patients receiving immunosuppressants for conditions other than nephrotic syndrome

During the same period as the above study, we conducted another prospective study of live attenuated vaccines among patients receiving immunosuppressants for conditions other than nephrotic syndrome [42]. Two months after a single dose, the antibody titer (mean ± SD) was 34.3 ± 39.1 for measles, 55.0 ± 67.6 for rubella, 7.0 ± 6.8 for varicella, and 7.1 ± 7.1 for mumps. Seroconversion rates were 80.0% for measles (8/10 vaccinations), 100.0% for rubella (15/15 vaccinations), 59.1% for varicella (13/22 vaccinations), and 69.2% for mumps (9/13 vaccinations). These results were comparable to those of the study of patients with nephrotic syndrome receiving immunosuppressive agents [36]. In the present study, one person developed varicella from the vaccine strain after varicella vaccination, and was hospitalized for additional treatment. However, this patient was treated before the current immune criteria (Table 4) had been set, and presented with: CD4$^+$ T cells, 511/mm^3; stimulation index

of lymphocyte blast transformation by PHA, 91.1; and serum IgG, 208 mg/dL. These findings would not meet the current criteria.

National survey on live attenuated vaccines in patients using immunosuppressive or biological agents

To enable the future use in society of live attenuated vaccines in patients receiving immunosuppressants, we conducted a national survey with the aim of revising the wording "contraindicated" on package inserts [44]. The primary survey was an institutional survey in which questionnaires were mailed to 480 institutions, receiving and analyzing responses from 415 institutions (86.5%). Of these, 13.8% of institutions administered live attenuated vaccines to patients receiving immunosuppressants, and 2.2% administered live attenuated vaccines to patients using biological agents. About two-thirds of institutions wanted to administer live attenuated vaccines even to patients receiving immunosuppressants. A secondary survey of patients was sent to 66 institutions, and information on 781 vaccinated patients was collected from 59 institutions (89.4%). Viral infections from the vaccine strain were seen in 2 patients (0.3%, both varicella), but no life-threatening adverse events were observed.

Current issues and future outlook for live attenuated vaccines in people receiving immunosuppressants

The prospective studies at our institution and past reports suggest the possibility that, under certain conditions, administration of live attenuated vaccines is safe and effective even in patients receiving immunosuppressants. However, patients receiving immunosuppressants include some with cellular immunodeficiency, who would thus face mortal danger from the high risk of vaccine-strain viral infections; in these patients, vaccination remains strictly contraindicated. Therefore, the immunological criteria enabling safe administration of vaccines among patients receiving immunosuppressants need to be investigated further.

Social adjustments also need to be made with the ultimate purpose of revising the descriptions in package inserts and guidelines for both immunosuppressants and live attenuated vaccines. Sharing information with related academic societies and experts and building a consensus, as well as maintaining close cooperation with the relevant regulatory authorities, will likely be necessary.

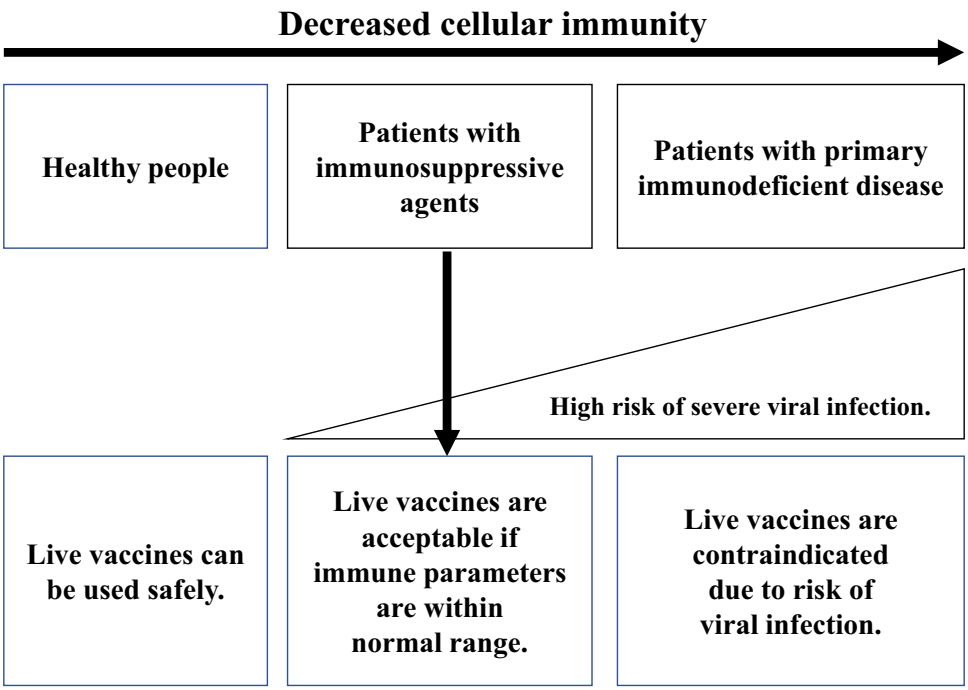

Fig. 1 Relationship between degree of immunodeficiency, risk of infection and safety of live vaccines

Conclusion

When vaccinating individuals with pre-existing conditions, the primary physician should always weigh the advantages and disadvantages when making vaccination decisions for individual patients. Factors for vaccination include a high risk to the patient in the event of contracting the disease the vaccine protects against (e.g., varicella in patients receiving immunosuppressants), a high risk of disease exacerbation with contraction of an infectious disease (e.g., recurrence of nephrosis after contracting influenza), and a high prophylactic effect from the vaccine. Factors against vaccination include the high frequency or risk of adverse reactions to the vaccine (which needs to be considered in individual patients), the high risk of vaccine-strain infection (e.g., live attenuated vaccines in patients with cellular immunodeficiency), the high risk of exacerbating pre-existing conditions with the vaccine, and the low prophylactic effect from the vaccine. These issues should not be decided uniformly, but instead need close consideration of the clinical course of the individual patient to date, their susceptibility to infection, the likelihood of adverse events after vaccination, and other factors.

Another important factor is the ratio of vaccinations in the general population. We should encourage healthy people to receive routine vaccinations thoroughly to protect immunocompromised patients from infectious diseases. In many countries, the system of routine vaccination is well developed and the vaccination rate is high, but there are many countries where the vaccination rate is low. Promotion and enlightenment of vaccination in healthy people might be crucial.

Finally, the relationships between the immune status of the patient and infection risk as well as the safety of live attenuated vaccines are shown in Fig. 1. The greater the decrease in immunity, the higher the risk of serious infection, which also makes administration of live attenuated vaccines difficult. For patients receiving immunosuppressants, immunological assessment of whether a live attenuated vaccine can be administered safely is important. For patients who can be vaccinated, administration of the vaccine during a period when the underlying disease is stable is preferable.

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Declarations

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