Live viral vaccines in transplanted patients

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Summary

Live attenuated viral vaccines (LAVV) have been used safely and with great success for decades to protect healthy patients against sometimes life-threatening diseases. The current recommendations usually contraindicate their use in immunocompromised hosts, despite an often increased risk for a severe presentation of disease. In this article, we review currently available LAVV, such as varicella-zoster, measles/mumps/rubella, influenza, polio, rotavirus, and yellow fever in patients with solid organ or hematopoietic stem cell transplantation. The current pediatric and adult experience with pre- and post-transplantation vaccination is discussed. To date, because of insufficient data, evidence-based recommendations to safely vaccinate transplant recipients are not available. Hopefully in the near future, specific recommendations will be implemented for certain LAVV in these patients.

Key words: vaccine; viral vaccine; live-attenuated vaccine; adverse effects; immunosuppression; organ transplantation; hematopoietic stem cell transplant; antibody; cell-mediated immunity; immunocompromised host

Introduction

Successfully used for more than 100 years, live vaccines contain live, but attenuated microorganisms, which are mostly viruses. There are essentially two ways to produce live attenuated viral vaccines (LAVV): by modifying the wild virus using repeated cultures and thus decreasing its virulence, or by using genetic re-assortment of a non-human virus (currently available LAVV in table 1). Viruses in LAVV, however, are still able to replicate inside the host [1]. Usually considered as safe, LAVV induce similar immune responses as wild-type microorganisms, including cell-mediated immunity (CMI), and in some cases induce a stronger immunogenicity and faster protection than inactivated vaccines, without the need of an adjuvant. Moreover, LAVV do not usually require booster doses and are cheaper to produce compared to inactivated vaccines. On the other hand, LAVV may interact with pre-existing specific antibodies (such as maternal antibodies) compromising their ability to induce an antibody response in certain patients (such as infants). They may also cause a vaccine virus-induced disease, which is a significant concern in transplant recipients [2].

The number of solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) patients has dramatically increased in the last decades: the patients also live longer and their lifestyle is closer to that of healthy individuals [3]. They are therefore more often exposed to vaccine-preventable microorganisms in the community. However, their chronic, iatrogenic immunosuppression can affect their B or T-cell response (or both), and consequently induce po or no antibody response to vaccination, as well as the loss of previously protective antibodies [4]. Some immune-modulators such as rituximab or mycophenolate mofetil are more strongly associated with reduced antibody responses [5–8]. Although rare (estimated, for example, as 1 out of 750’000 live poliovirus vaccines administration in the healthy population [1]), reversion to virulence is feared. This could lead to a possibly uncontrolled replication of the vaccine virus and, as a consequence, to a disease more severe than with community-acquired infection [9, 10]. This review examines the currently available literature on LAVV in SOT and HSCT recipients.

Varicella-Zoster virus vaccine

Varicella-zoster virus (VZV) is the aetiologic agent of chickenpox, a usually benign childhood disease. Serious complications are rare in healthy patients but may affect up to 10% of SOT recipients, with a mortality rate of 5–34% [11–13]. Immunocompromised patients usually require an intravenous antiviral treatment when VZV infection is recognised, as well as pre-emptive treatment with antivirals with or without specific intravenous immunoglobulins when exposed to disease [14]. The VZV vaccine was licensed in the US in 1995, but was developed by Takahashi et al. during the 1970s using the Oka strain [15]. Since then, its efficacy to decrease varicella-related hospitalisations in patients >1 year of age has been recognised [16]. Aiming to reduce the incidence of zoster and the post-herpetic neuralgia, in 2006 the FDA also authorised a live-attenuated vaccine against shingles (herpes zoster). This vaccine, which is only recommended in previously immune patients over 50 years of age, contains 14 times more plaque-forming units (PFU) than the varicella vaccine [17, 18]. Neut-
eralising antibodies are a good surrogate marker of protection against VZV, whereas they do not necessarily correlate with protection against shingles, where CMI plays a major role [19–21]. The zoster vaccine is licensed in Switzerland. As large studies are lacking concerning the VZV vaccine’s efficacy and safety in SOT recipients, the VZV vaccine is currently contraindicated after SOT by most medical societies and experts, but encouraged before transplantation when possible (i.e., age >9 months-old) if the patient is seronegative [22–26]. Seroprotective titres after immunisation of transplant candidates are usually obtained in a large proportion of patients [27–29]. Table 2 reviews the American Society of Transplantation’s (AST) recommendations for pre- and post-transplantation immunisation, as well as antibody titres monitoring. A number of smaller studies have reported their experience in vaccinating patients after SOT [19, 27, 30–35]. Most of these patients were paediatric liver transplant recipients, at least 6 months after SOT, with stable organ function, and low dose immunosuppression. There was no efficacy or safety issue reported: seroconversion rates varied between 65% and 100% (table 3), and side effects were similar to the healthy population. When a follow-up of antibody titres was reported, they waned moderately, and breakthrough disease was rarely reported [36–38]. In our institution, VZV-specific CMI also increased significantly after immunisation, in a cohort of 36 paediatric liver transplant recipients [34]. Zoster vaccine is currently contraindicated after SOT (table 2), but studies are ongoing to evaluate its safety in adult kidney transplant recipients [25, 26]. In HSCT recipients, seronegative patients should be vaccinated before transplantation when possible [2], without a defined ideal time frame between vaccination and conditioning. Most recommendations suggest waiting at least 2 years between HSCT and immunisation: high seroconversion rates and low adverse events are then reported [39, 40]. However, one study also showed increasing CMI in all patients who where immunised 3–4 months after HSCT, but results were not significant [41]. Interestingly, Chou et al. could not demonstrate a difference in response between recipients of a matched-related or alternative donor graft, or between patients given a T cell-depleted or T-replete alternative donor graft [39]. Even if theoretically possible because of viral shedding, there is little or no risk of virus transmission from a recently immunised contact to a SOT or HSCT recipient [25]. Therefore, immunisation of VZV seronegative individuals close to SOT or HSCT patients is strongly encouraged [25, 42].

**Measles, mumps and rubella vaccine**

Measles is a severe disease, with acute complications, such as severe pneumonia and measles-associated encephalopathy, or late-onset complications, such as sub-acute sclerosing panencephalitis. These complications can occur in immunocompetent as well as immunocompromised patients. Severe complications after measles infection have been reported in SOT patients [43–45]. The measles vaccine (Edmonston B strain) was developed in the 1950s, licensed in the 1960s and is nowadays recommended in most countries’ vaccination plan, often combined with mumps and rubella vaccines (called MMR vaccine). A genetic component to explain differences in antibody production between individuals in response to MMR vaccination has been suggested [46, 47]. The MMR vaccine has been shown to be immunogenic in transplant candidates and no serious adverse events have been reported.

<table>
<thead>
<tr>
<th>Table 1: Currently available live-attenuated viral vaccines and used definitions in vaccinology.</th>
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<td><strong>Live viral vaccines</strong></td>
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<th>Table 2: Recommendations concerning immunisation before and after solid organ transplantation and monitoring of vaccine titres.</th>
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<td><strong>Live vaccine</strong></td>
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<tr>
<td><strong>Children</strong></td>
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<tr>
<td>VZV</td>
</tr>
<tr>
<td>Zoster</td>
</tr>
<tr>
<td>MMR</td>
</tr>
<tr>
<td>Influenza (LAIV)</td>
</tr>
<tr>
<td>Rotavirus</td>
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<tr>
<td>Yellow Fever</td>
</tr>
<tr>
<td>Vaccinia</td>
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SOT: Solid organ transplantation; VZV: Varicella-Zoster Virus; MMR: Measles-Mumps-Rubella; LAIV: Live Attenuated Influenza vaccine; NA: not applicable

Adapted from [23]
In SOT recipients, however, but only in small paediatric studies (N ≤35), the seroconversion rate was lower after SOT (range 41–100% for the measles component) but appeared to be safe in specific conditions, which included low immunosuppression (table 3) [27, 32, 33, 35, 36, 50]. However, recommendations still contraindicate its use in SOT patients (table 2) [25, 26].

Loss of immunity is frequent in previously seropositive HSCT patients, especially in children. In case of outbreaks, immunisation with the measles vaccine could be considered in patients without chronic graft versus host disease (GVHD) or ongoing immunosuppression [51]. Experts recommend immunising with MMR vaccine two years after HSCT [2, 52]. However, children have been immunised earlier in outbreak settings: all naïve children seroconverted and most patients with protective albeit low specific IgG titres <200 UI/ml showed a >4–fold increase in titres. Only mild adverse events were reported [53].

Almost no data is available for the mumps and rubella part of the MMR vaccine in immunosuppressed hosts, probably because of the low risk of severe mumps disease and the fact that the rubella vaccine is mainly administered to avoid congenital disease in pregnant women. Among a cohort of 15 paediatric liver transplant recipients immunised after transplantation, seroconversion rates for mumps and rubella were 100% [27].

Influenza vaccine

Up to 50 million cases of influenza occur yearly in the US [54]. Seasonal yearly immunisation is currently the only effective strategy to prevent and control influenza [55], and it is recommended for all patients older than 6 months in the US. In other countries, yearly vaccination is only recommended to certain patients especially at risk for severe disease, or people close to patients such as healthcare workers.

Two types of vaccines are available at this time: an inactivated trivalent influenza vaccine (ITV) and a live-attenuated influenza vaccine (LAIV). ITV is used in the general population in most developed countries and is currently the only influenza vaccine recommended in transplanted and other immunocompromised patients [55]. Initially licensed in 2003 in the US for healthy patients 5–49 years old [56], LAIV is safe and immunogenic in this population [57–65]. The intranasal administration allows viral replication in the nasal mucosa [66], but not in the lungs because of the higher temperature in the lower respiratory tract [67, 68]. The administration route avoids painful injections, and induces a mucosal immunity that more closely resembles natural infection [69–72]. Unlike ITV, antibodies are not a reliable correlate for protection after LAIV [55]. IgA mucosal immunity [69–72] as well as CMI [73, 74] are better correlates for LAIV protection. Clinically, LAIV seems more effective than ITV in children [57, 58, 75], but not in adults [57, 64, 65, 75–77], with no difference regarding adverse events. LAIV may also provide longer protection than ITV [78], and possible cross-protection against non-vaccine serotypes [64, 75, 79].

SOT recipients with influenza illness are at high risk for severe influenza [80, 81]; they benefit from annual immunisation. Current recommendations contraindicate the use of LAIV in these patients, but recommend ITV (table 2) [25, 82–84]. Yearly ITV immunisation is recommended 4–6 months after HSCT, and LAIV is also contraindicated in HSCT patients and their household contacts [2, 51, 52, 85]. LAIV is currently not licensed in Switzerland.

Polio vaccine

Two forms of the polio vaccine are available: an injected inactivated polio vaccine (IPV or Salk vaccine), introduced in 1955, and an oral live-attenuated polio vaccine (OPV or Sabin vaccine), introduced in 1961 [86]. Most countries used OPV to eradicate polio because it was cheaper and easier to administer, induced longer immunity with a component of mucosal immunity, and provided indirect protection through viral shedding. When cases of vaccine-associated paralytic poliomyelitis (VAPP) outnumbered cases of wild polio after an effective mass OPV immunisation, recommendations changed: IPV is currently used in most countries for all patients, whether immunocompromised or not [87–89]. Due to outbreaks still occurring in some countries in Africa and Asia, OPV is still recommended in a few endemic countries or in countries in which there is an increased risk of import and subsequent spread [86, 90]. Due to the risk of VAPP, OPV is contraindicated in immunosuppressed patients or in their household contacts [91–93]. Therefore, OPV is also contraindicated in SOT recipients [84, 94]. IPV alone is recommended 6–12 months after HSCT and in household contacts [2, 51, 52, 85, 95]. OPV is not licensed anymore in Switzerland.

Table 3: Interventional studies on VZV and MMR immunisation in solid organ transplant recipients.

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Type of patient</th>
<th>Type of organ</th>
<th>Number of patients</th>
<th>Vaccine</th>
<th>Best seroconversion rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rand, 1993 [50]</td>
<td>Paediatric</td>
<td>Liver</td>
<td>18</td>
<td>Measles or MMR</td>
<td>41% measles</td>
</tr>
<tr>
<td>Zamora, 1994 [30]</td>
<td>Paediatric</td>
<td>Kidney</td>
<td>17</td>
<td>VZV</td>
<td>75% VZV</td>
</tr>
<tr>
<td>Kano, 2002 [27]</td>
<td>Paediatric</td>
<td>Liver</td>
<td>15</td>
<td>MMR / VZV (re-immunisation)</td>
<td>85% Measles 100% Mumps / Rubella 71% VZV</td>
</tr>
<tr>
<td>Chaves, 2005 [19]</td>
<td>Paediatric</td>
<td>Kidney</td>
<td>6</td>
<td>VZV</td>
<td>67% VZV</td>
</tr>
<tr>
<td>Weinberg, 2008 [31]</td>
<td>Paediatric</td>
<td>Liver/Intestine</td>
<td>16</td>
<td>VZV</td>
<td>87% VZV</td>
</tr>
<tr>
<td>Khan, 2006 [32]</td>
<td>Paediatric</td>
<td>Liver</td>
<td>26 MMR / 31 VZV</td>
<td>MMR / VZV</td>
<td>73% Measles 65% VZV</td>
</tr>
<tr>
<td>Shinjoh, 2008 [33]</td>
<td>Paediatric</td>
<td>Liver</td>
<td>18</td>
<td>MMR / VZV</td>
<td>100% Measles, Rubella 87% VZV</td>
</tr>
<tr>
<td>Posafay-Barcode, 2012 [34]</td>
<td>Paediatric</td>
<td>Liver</td>
<td>36</td>
<td>VZV</td>
<td>100% VZV</td>
</tr>
<tr>
<td>Levitsky, 2002 (case report) [37]</td>
<td>Adult</td>
<td>Liver</td>
<td>1</td>
<td>VZV</td>
<td>Post-exposure vaccine: disease</td>
</tr>
<tr>
<td>Kraft, 2006 (case report) [38]</td>
<td>Adult</td>
<td>Heart</td>
<td>1</td>
<td>VZV</td>
<td>Post-vaccine disease</td>
</tr>
</tbody>
</table>

VZV: Varicella-Zoster virus; MMR: Measles-Mumps-Rubella; SOT: Solid organ transplantation.
Rotavirus vaccine

Rotavirus is one of the leading causes of diarrhoea worldwide, with about 500,000 yearly deaths among young children, 90% of them in developing countries [96, 97]. Protection against rotavirus depends on humoral and CMI [98]. In immunosuppressed patients, rotavirus disease is usually not associated with severe or prolonged diarrhoea [96]. Two oral LAVV directed against rotavirus surface proteins are available and induce viral replication in the gut. All doses for both vaccines need to be administered before the age of 8 months. A recent Cochrane review reported that vaccine efficacy is lower in countries with high mortality rates, but because of the burden of disease, the absolute benefit remains high [99]. The World Health Organization (WHO) recommends including the rotavirus vaccine in the global immunisation schedules in countries with high mortality rates [96] for all children without prior HIV testing but some experts recommend avoiding this vaccine in known, symptomatic HIV+ children [100]. In several European countries and in the US, the vaccine has been included in national immunisation schedules [101]. In Switzerland however, because of a cost-benefit ratio which was unfavourable and a reluctance of primary care physicians to introduce a new vaccine in an already crowded schedule, the introduction of this vaccine in the national recommendations was declined by the Swiss Federal Committee for Immunisations. For SOT (table 2) and HSCT recipients little data are available, probably because rotavirus disease affects mainly very young children. The vaccine is however contraindicated in these patients [25, 52]. The Centers for Disease Control and Prevention (CDC) recommends rotavirus vaccine use in immunodeficient patients with caution and the WHO contraindicates it in severely immunosuppressed patients [96, 101]. More studies are needed to determine safety and immunogenicity of rotavirus vaccine in this population.

Yellow fever vaccine

Yellow fever is a severe viral haemorrhagic fever caused by an arbovirus transmitted through Aedes mosquito bites in sub-Saharan Africa and South America. The LAVV is the only available vaccine and is recommended in all patients in the yellow fever endemic areas from 9 months of age, except for severely immunosuppressed patients [102]. In developed countries, the yellow fever vaccine (YFV) is contraindicated in immunosuppressed patients [93]. Major complications of the YFV are vaccine-associated viscerotropic disease, and neurologic disease that occur in 0.4 and 0.8 cases per 100,000 doses, respectively. In countries endemic for yellow fever or patients living in countries endemic for yellow fever, or patients planning to travel in endemic countries in the future (work, leisure) should be immunised before SOT whenever possible, as YFV is permanently contraindicated after SOT, and antibody response may be decreased by immunosuppressive therapies (table 2) [25, 26, 103]. Experts recommend checking seroprotection after SOT in previously immunised patients if travelling is planned: medium to long term persistence of antibodies against yellow fever has been identified after SOT [104]. Among a cohort of 19 SOT patients inadvertently immunised against yellow fever, the only reported side-effect was a mild reaction at the injection site [105]. Time between transplantation and YFV ranged between 3 to 340 months (mean 65 months, median 36 months). However, more studies are needed to evaluate safety of YFV in SOT patients. In HSCT recipients, YFV is contraindicated and patients should be discouraged from travelling to endemic area. Only case-reports describe safe and immunogenic immunisation in this population [106, 107]. However, the risk/benefit balance may favour immunisation for HSCT patients travelling or living in endemics areas; YFV can therefore be considered >2 years after HSCT in patients without immunosuppression, GVHD, or recurrent malignancy [2, 52, 95, 102].

Vaccinia (smallpox)

Smallpox was caused by variola virus and had a high mortality rate (1/3 of cases). Thanks to vaccination, it was officially eradicated in 1979. Since then, threats of biological warfare have regularly re-emerged, and vaccines against smallpox have been administered pre-emptively to selected populations. There are no studies in SOT recipients, and the smallpox vaccine is not recommended in immunosuppressed individuals because of a high risk for severe, life-threatening disease secondary to vaccinia viremia (table 2) [25, 108, 109]. However, SOT experts recommend immediate smallpox vaccination in case of “face-to-face” contact with a case of confirmed smallpox [25].

General considerations are pre-transplantation assessment and post-vaccine monitoring

During the pre-transplantation assessment, the patient should have a complete documented vaccine history and serological control to ensure VZV and MMR protective titres before transplantation. Catch-up immunisation must be performed in case of low or absent antibody titres, with a subsequent serological control 4 to 6 weeks later and re-vaccination if needed. Proof of seroconversion and regular serological follow-up is usually recommended after transplantation for VZV and MMR (children), or VZV only (adults) (table 2) [25]. In our opinion, MMR serologies should also be checked in adults in countries in which measles, for example, is endemic or epidemic. While antibody concentration above a predetermined threshold can be insufficient to protect against disease, we currently have no better marker of protection. It is important to follow over time that protective antibody levels are maintained, because antibody waning has been recognised [4]. In our institution, we monitor antibody levels at least once a year after transplantation, which could be increased in case of exposure. To increase herd immunity and improve passive protection, experts currently recommend VZV (in case of negative history) and MMR immunisation, as well as yearly influenza vaccination (use TIV and avoid LAIV whenever possible).
Dengue fever is widespread worldwide and has a broad range of manifestations, from non-specific viral disease to severe haemorrhagic symptoms. As with yellow fever, the disease is due to a flavivirus transmitted through Aedes mosquito bites. A LAVV against dengue fever (CYD-TDV) has been evaluated in phase I and II studies with encouraging safety and immunogenicity profiles in healthy adults and children [110–117]. No study currently reports results of dengue vaccine in immunosuppressed patients. New vaccines, such as a CMV vaccine or vaccines against other herpes viruses, as well as a universal influenza vaccine would be useful, but it is unlikely at this point that they will be LAVV.

Further studies are also needed to determine different criteria for safe LAVV administration: it is, for example, important to identify the best timing for immunisation: is it 6–12 months or 12 months after transplantation? It is also important to clearly define “low immunosuppression” using measurable criteria, such as lymphocytes count or CD4 T-cell count, immunosuppressive or immunomodulating drugs dosing (steroids, tacrolimus, ciclosporine, mycophenolate mofetil, monoclonal antibodies), and time since receiving immunoglobulins. Host factors, potentially an important factor in immune response, have also been studied for example in genome-wide association studies [118, 119].

Conclusion

Despite encouraging results, there is not enough evidence to date to safely recommend routine use of LAVV in transplant recipients. For these reasons, it is paramount to immunise with LAVV before transplantation whenever possible, to confirm seroconversion, and to follow antibody titres thereafter. More studies are needed to evaluate seroresponse and specific CMI, kinetics of immune responses, and long-term protection, as well as best circumstances for immunisation (timing, immunosuppression). It is possible that LAVV will be recommended in the future after transplantation in well-defined patients.

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