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PERSPECTIVE

Concerns on Vaccine against Varicella Caused by Varicella-Zoster Virus Infection

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Varicella-zoster virus (VZV) belongs to a neurotropic *Alphaherpesvirinae* and is the causative pathogen of both the varicella and herpes zoster. Currently, there are three different vaccines for the prevention, low does live-attenuated Oka (vOka) against varicella, high does vOka and glycoprotein E with the AS01B adjuvant system against zoster. Varicella vaccine containing vOka effectively prevents varicella, but latency of vOka can be detected in the inoculated population and its reactivation causes zoster. Reducing virulence of vOka is a potential way to prevent vOka reactivation from latency, or transport from infected neuron to neighbor neurons and the innervated dermatome, which causes herpes zoster. Therefore, to develop better/safer vaccine that can not only prevent varicella, but also avoid herpes zoster is required. In addition, change one-dose varicella vaccination to two-dose schedule will help to prevent varicella breakouts in primary schools.

VZV Infections and Diseases

Primary VZV infection mainly occurs in children and causes varicella (chickenpox). The systemic vesicular rash is led by T cell-associated viremia. After onset of varicella the virus remains as latent infection in the dorsal root ganglion for life-long time. Years later when the host's immunity decreases, or host is immunocompromised by immune suppressors, VZV can be reactivated and cause herpes zoster (shingles) (Arvin 2013). Some herpes zoster company with postherpetic neuralgia (PHN), which lasts over 90 days. There is no efficient treatment for PHN (Argoff *et al.* 2004; Jeon 2015), and patients become addict to pain killer or other addiction issues and psychological problem (Whitley *et al.* 2010).

vOka, a live-attenuated vaccine licensed in several countries, developed by Takahashi and his colleges in Japan in 1974 (Takahashi *et al.* 1974), has been safely and effectively used to guard against varicella. However, diseases caused by VZV still occur both in developing countries where VZV infection is less concerned, and developed countries where a routine varicella vaccination has already been done for decades. The incidence rate of herpes zoster increases and occurs younger. In addition, vaccine-associated herpes zoster has also observed (Galea *et al.* 2008; Yoshikawa *et al.* 2016). It is far away from eradication of VZV infections and the diseases.

Varicella Vaccine and Vaccination

Varicella is present worldwide and often occurs more prominent in winter and spring (Gershon *et al.* 2015). It is a self-limiting disease with widespread vesicular rash and finished by fever, but occasionally followed by serious complications including encephalitis, hepatitis, pneumonia, bacterial sepsis and hemorrhage. These serious complications often occur in infants, aged adults, and severely immunocompromised individuals. Maternal varicella suffered during the first twenty weeks of pregnancy may cause severe embryopathies too (Pastuszak *et al.* 1994).

The most widely used varicella vaccines consist of the Oka strain of live-attenuated VZV (vOka), 1350 PFU/dose, which is recommended by WHO since 1983. Over 10 years

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after Takahashi and his colleges developed live-attenuated varicella vaccine, vOka was first licensed in Germany and Sweden in 1984, Japan and Korea in 1988, USA in 1995, and China in 1998. The studies on safety and efficacy of this vaccine in healthy children showed that it is safe with persisting immunity (Asano *et al.* 1985, 1994). Another study in the USA showed varicella vaccine efficacy of 100% at 1 year, 98% at 2 years, and 92% in households (Weibel *et al.* 1984). A comprehensive 22-year review in USA showed that varicella cases and varicella-related deaths declined obviously since varicella vaccines' introduction in 1995 (Woodward *et al.* 2019). All these studies support that vOka vaccination is highly effective to prevent varicella.

A 10-year safety evaluation on varicella vaccination from 1995 to 2005 worldwide was conducted by Merck Company, reported 697 herpes zoster cases (4.2% of total adverse events, 697 cases among a 16,683 population). Among them 57 cases were vaccine-associated herpes zoster and 38 were caused by wild type VZV herpes zoster identified by PCR (Galea *et al.* 2008). Similarly, varicella vaccine safety review from 2005 to 2015 was performed in Japan. It identified 10 vaccine-associated herpes zoster and 25 wild type VZV herpes zoster among the 66 herpes zoster cases, which takes for 18.8% of adverse events (Yoshikawa *et al.* 2016). In another study on herpes zoster incidence after varicella vaccination from 2005 to 2009 in the USA, among 83 herpes zoster cases, 38 were vaccine-associated herpes zoster and 42 were wild type VZV herpes zoster (Weinmann *et al.* 2013). All these data indicate that live-attenuated vOka may establish latency and reactivate to cause herpes zoster in varicella vaccine vaccinated population. Deal with the live-attenuated vOka vaccine associated adverse events and develop better vaccine is required.

Despite one-dose varicella vaccination has been shown to be highly effective to reduce incidence of severe disease, but breakout infections are still commonly observed among vaccinated children in daycare and primary schools. From 2006 to 2017, 265 varicella outbreaks involving 3263 schoolchildren which was 88.1% vaccinated with one-dose varicella vaccine were reported in Shanghai, China (Wu *et al.* 2019). One-dose varicella vaccine even with high coverage is insufficient to prevent school outbreaks. Compare to one-dose schedule who receive two-dose vaccine achieved higher seroconversion rates and a higher antibody titer among subjects (Schuster *et al.* 2008). Therefore, the Centers for Disease Control and Prevention recommended a two-dose varicella vaccination schedule in the USA in 2006. The two-dose varicella vaccination schedule has been applied since 2014 in Ningbo city, China. A study about two-dose varicella vaccination effectiveness showed that the total varicella incidence was 0.37% for all the vaccinated children and as low as 0.04% for the two-dose vaccination (Pan *et al.* 2018). And regardless of the timing of the second dose varicella vaccination, Chinese healthy children can tolerate the vaccine well (Deng *et al.* 2016). The better protection efficiency and further lower varicella incidence will help the CDC to support the two-dose vaccination policy. However, considering the cost-effectiveness, some countries still implement the one-dose schedule.

Herpes Zoster Vaccine

Herpes zoster caused by reactivated VZV is estimated around 30% of human being over their lifetime (Johnson *et al.* 2015b). In the developed countries, zoster incidence increases slowly over time that predates the introduction of varicella vaccine and may relate to changing social or environmental conditions. Postherpetic neuralgia, a neuropathic pain, is the most common complication of herpes zoster that persists for more than three months after eliminating rash, and incidence of postherpetic neuralgia increases with aged 50 and individuals with severe immunosuppression (Johnson *et al.* 2015a; Forbes *et al.* 2016). Other possible sequelae of herpes zoster with lesser frequency than postherpetic neuralgia include VZV meningitis, cerebellitis, meningoencephalitis and vasculopathy. Herpes zoster usually occurs in adults over the age of 50 due to immunosenescence naturally or in those who are immunocompromised. The symptom presents as a painful, vesicular rash and negatively affects patients' quality of life, especially when complications occur.

There are two available zoster vaccines, Zostavax (Merck) was licensed in 2006 and Shingrix (GSK) was licensed in 2017 by the US FDA. Zostavax uses a higher concentration of live-attenuated Oka to prevent zoster with a single-dose, containing a minimum potency of 19,400 PFU/dose versus varicella vaccine, which is 1350 PFU/dose. A Zostavax efficacy trial was done from 1998–2001. A total of 38,546 subjects aged 60 years and over were evaluated in the USA, the Zostavax vaccine cut down the incidence of herpes zoster by 51% and postherpetic neuralgia by 67% (Oxman *et al.* 2005). Zostavax shows different effects in different age groups, 63.9% prevention of herpes zoster for 60–69-year ages compared to 37.6% for 70 years and over. The decline of the vaccine's protective effect may be due to the older people have less VZV-specific T-cells with vOka vaccination. Another study was performed in North America and Europe from October 2007 to January 2010. The efficacy, safety and tolerability were confirmed, and among the 22,439 aged 50–59 year-old subjects, the vaccine efficacy for preventing zoster was 69.8% and the vaccine was well tolerated (Schmader *et al.*

2012). These data suggest that Zostavax should be vaccinated younger than 60 years old.

Shingrix is a recombinant subunit vaccine which contains VZV glycoprotein E (gE) and AS01B adjuvant system (Lal *et al.* 2015). VZV gE is the most abundant glycoprotein both in virions and infected cells, which is also involved in viral replication and cell-to-cell spread (Arvin 2013). It was selected as the vaccine antigen due to it's a major target of the VZV-specific T-cell response and can strongly promotes humoral and $CD4^+$ T cell-mediated immunity. As now, two phase 3 trials for Shingrix had been tested, two doses of Shingrix were given to two groups of people over 50 and over 70, respectively. Vaccine efficacy against zoster was 97.2% for adults aged $\geq$ 50 years with a mean follow-up period of 3.2 years (Lal *et al.* 2015) and 89.8% for these aged $\geq$ 70 years with a mean follow-up period of 3.7 years (Cunningham *et al.* 2016). Data from these two trials show that vaccine efficacy against postherpetic neuralgia was 88.8%. Overall, Shingrix effectively reduced the risk of herpes zoster and postherpetic neuralgia among these aged $\geq$ 50 years, but further long-term clinical efficacy follow up studies should be done.

Both Shingrix and Zostavax are based on the strategy to reboots the existed specific immunity to prevent the herpes zoster and its complications, including postherpetic neuralgia.

Future Perspectives

Currently, there are three vaccines for preventing diseases caused by VZV infections. Varicella vaccine is 1350 PFU/does live-attenuated vOka; herpes zoster vaccines include Zostavax, 19,400 PFU/does live-attenuated vOka, and the other one, Shingrix, glycoprotein E with the AS01B adjuvant system.

Varicella vaccine contains live-attenuated vOka, effectively prevents varicella, but virus can establish latency which is detected in vaccine inoculated population and its reactivation causes zoster. To prevent the adverse events from vaccine, a novel neuro-attenuated varicella vaccine is required, which can not only effectively prevent varicella, but also avoid herpes zoster upon its reactivation. Potential candidates include vOka deficient of ORF7, or ORF65, or ORF36. ORF7 of VZV has been identified as a neurotropic factor, deletion of ORF7 attenuates virus replication in epithelial cells and neurons (Selariu *et al.* 2012; Jiang *et al.* 2017). VZV ORF65 is a homologue of HSV-1 US9, related to the transport of virus in axons, maybe another target for reducing virulence of VZV in neuron (Miranda-Saksena *et al.* 2015). VZV ORF36 encodes thymidine kinase, a homologue of HSV-1 UL23, which is essential for virus replication in neuron (Lo and Anderson 2011; Zeng *et al.* 2017). ORF36 deletion VZV can't reactivate and replicate in neurons, as a vaccine without risk for herpes zoster. Moreover, change one-dose varicella vaccination to two-dose schedule will help to prevent varicella breakouts in adolescent.

In addition, the incidence of herpes zoster has been increasing since Shingrix licensed for two years without long-term clinical efficacy studies, and Zostavax has not been widely used due to its virulence. In order to improve the acceptance of Shingrix, long-term clinical efficacy and safety studies should be confirmed in a larger population and a wider area. We can also delete ORF7 of vOka which are important for virus replication in epithelial cells and neurons, to reduce the virulence of Zostavax. We predict that when the varicella vaccine is improved, for example the vaccine virus can't transmit to other neuron (ORF7 deletion and defect in secondary envelopment) or other modifications to limit virus replication, then the herpes zoster will in turn be reduced.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Animal and Human Rights Statement This article does not contain any studies with human or animal subjects performed by any of the authors.

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