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Review

The vaccines for Bovine Herpesvirus Type 1: A review

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Bovine herpesvirus type 1 (BoHV-1) is the pathogen of Infectious Bovine Rhinothracheitis (IBR) disease, causing great economic losses in the livestock industry. Vaccine is a powerful means to control the virus. Here, the review described the currently available knowledge regarding to the advance in the field of BoHV-1 vaccine including the marker vaccines, DNA vaccines, subunit vaccines and the recombinant virus vaccines.

Key words: BoHV-1, vaccine, DIVA, recombinant virus.

INTRODUCTION

BoHV-1 is the causative agent of respiratory infection (infectious bovine rhinotracheitis), genital infection (infectious pustular vulvovaginitis), conjunctivitis and systemic infection, leading to abortion and fetal deaths (OIE, 2008; Thiry et al., 2008, 2009). The infected cattle may be predisposed to secondary opportunistic infections which results in severe bacterial pneumonia (Li et al., 1995). Once infected, virus latency normally occurs, and the antibody response seems to be life-lasting, thus the sero-positive animals should be considered as potential carriers and intermittent shedder of the virus, with the exception of young calves with passive maternal antibody and non-infected cattle vaccinated with killed vaccines (OIE, 2008).

BoHV-1 infection is worldwide distributed affecting domestic and wild ruminants (Del et al., 2009). And it has caused significant economic losses in cattle industry. However, after the implementation of strict BoHV-1 control programs, the disease had been eradicated from Nordic European countries (Norway, Finland and Sweden), Austria, Denmark, and part of Italy. Currently, other European countries are under compulsory or voluntary eradication programs, all involving the application of inactivated or live “marker”vaccines. In most of the country, classical attenuated and killed BoHV-1 vaccines are commonly applied (Ackermann, 2006).

Currently, safe and effective vaccines against BoHV-1 are not available. The inactivated vaccines are usually poor immunogens and may cause clinical disease if insufficiently inactivated. On the other hand, live vaccines may cause latent infection and immune suppression (Yates, 1982). So the existing problems and apparent inability to control BoHV-1 infections through these vaccination approaches promoted the development of alternative vaccination strategies against BoHV-1. Genetic engineering is considered to be a potential method to resolve the matters and had been employed to improve the efficiency of BoHV-1 vaccine.

MARKER VACCINES USED FOR DIFFERENTIATING INFECTED FROM VACCINATED ANIMALS (DIVA)

BoHV-1 belongs to the alphaherpesviruses. The genome of alphaherpesviruses encodes for 9-11 glycoproteins. Some glycoproteins like gB and gD are essential for viral replication (Fehler et al., 1992). At least four glycoproteins (gC, gG, gI and gE) are non-essential for in vitro replication, but they do play a role in the in vivo phenotype (Schwyzer et al., 1996). Except for the gC deletion mutant, these deletion mutants are significantly less virulent in vivo (Kaashoek et al., 1998).

For both trade and surveillance purposes, it is important not only to differentiate naturally infected and vaccinated ruminants, but also to identify vaccinated animals that become infected with BoHV-1. So the DIVA strategy had been introduced and applied to develop the vaccine of BoHV-1. For the virus of BoHV-1, the complex of gE and gI is not involved in the entry of extracellular

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particles (Rebordosa et al., 1996; Yoshitake et al., 1997) and hence viral gE deletion mutants display unimpaired penetration kinetics and virus yields in cell culture (Rebordosa et al., 1996). Thus, the marker vaccines were usually based on the deletion of BoHV-1 gE. Furthermore, deletion of BoHV-1 gE is generally associated with a marked reduction in the virulence, thus facilitates the generation of live attenuated vaccine (van Engelenburg et al., 1994).

Many years ago, gE-deleted BoHV-1 had been developed both in a killed virus and a modified live virus marker vaccine for DIVA strategy (Strube et al., 1996). In 1997, a comparative study was carried out to evaluate the efficacy of a live gE-deleted vaccine and an inactivated gE-deleted vaccine. They concluded that the inactivated marker vaccines are more efficacious in reducing virus excretion after reactivation than a live marker vaccine (Bosch et al., 1997). But the live gE-deleted vaccine could induce early immunity against a BoHV-1 contact infection, when the vaccine was intranasal administrated. This suggests that this vaccine can be used efficaciously at the early stages of a BoHV-1 outbreak (Kaashoek and van Oirschot., 1996). And further study implicated that the live BoHV-1 marker vaccine is not shed after intramuscular vaccination. Therefore, it is recommended to apply the gE-deleted live vaccine by the intramuscular route in situations where it is undesirable that the vaccine virus is excreted (Makoschey and Beer, 2007).

gD SUBUNIT VACCINE

The glycoprotein gD is a high immunogenetic protein which can induce protective antibody of high titer. It was found that immunization with full-length gD or a truncated, secreted form of gD (tgD) produced using a vaccinia virus expression system, could developed significantly higher neutralizing antibody titers in the serum and nasal mucosa than animals vaccinated with killed virus or modified live virus. In addition, the gD and tgD-immunized animals experienced minimal weight loss and virus shedding post-challenge. The date indicated that when formulated in an appropriate adjuvant, gD subunit vaccine is more effective than the killed virus or modified live virus vaccines and may be used as a marker vaccine for concurrent vaccination and eradication programs of BoHV-1 (van Drunen Littel-van den Hurk et al., 1997).

DNA VACCINE

Although, those inactivated and live attenuated vaccine have been widely used and contributed greatly to the control of virus transmission, better and safer vaccines are needed. DNA immunization is an approach which could improve the safety and the efficacy of vaccination. The use of DNA vaccination for BoHV-1 has shown promising results in mice, but a DNA vaccine showing great protection from the virus infection in calves had not been reported.

Viral surface glycoproteins of BoHV-1 have been identified as the main targets for protective humoral and/or cell-mediated immune responses and they have been selected as candidate antigens in DNA immunization. Glycoproteins B, C and D of BoHV-1 had been tested to evaluate their safety and efficacy with disappointing results in large animals.

In order to improve the immunogenicity of the DNA vaccines, novel adjuvant approaches like the incorporation of CpG oligodeoxynucleotides (ODN) had been proved for their ability to enhance immune responses against viral antigens (Mutwiri et al., 2008). The cytokine profile induced by CpG motifs is generally preferential for a Th1-type immune response (Babiuk et al., 2003). Ubiquitin is responsible for intracellular protein degradation and the production of peptides for the direct presentation via MHC class I. Hence, enhance the cell-mediated immune response to the vaccine antigens (Gupta et al., 2001).

In a previous study, Castrucci et al (2004) tested a candidate BoHV-1 DNA vaccine composed of a plasmid encoding epitopes of a single antigen encoded by the gD gene. Unfortunately, that vaccine did not protect the calves against infection with virulent BoHV-1. Subsequently, other DNA vaccines against BoHV-1 were evaluated for their efficacy in calves (Petrini et al., 2009). In their research, 12 copies of the CpG hexamer (GTCGTT) and Ubiquitin were used as the adjuvant molecules. Their data indicated that vaccination of calves with a DNA vaccines expressing tgD of BoHV-1 combined with GpG motifs has been able to prime the immune system. However, this response was able to protect only partially animals from virulent BoHV-1 challenge. And the gD protein expressed in fusion with the ubiquitin adjuvant molecules was not able to stimulate any immune response. These studies indicated that such adjuvant molecules could not work as expected in the development of DNA vaccine.

However, another research group found that the plasmid encoding a secreted truncated version of gD formulated with CpG, effectively primed the immune system of newborn lambs, whereas without CpG the tgD protein was less effective. Furthermore, a heterologous DNA prime-protein/CpG boost induced strong and balanced protective immune responses in newborn calves with BoHV-1-specific maternal antibodies (van Drunen Littel-van den Hurk et al., 2008). Obviously, the DNA vaccine combined with CpG motif is appropriate for the application in newborn lambs with maternal antibodies.

NDV VECTORED VACCINES

It had been confirmed that NDV can be used as a vaccine vector in non-avian hosts. NDV is attenuated in

non-human primates, and likely in other non-avian species, due to a natural host range restriction (Bukreyev et al., 2005; DiNapoli et al., 2007). NDV is antigenically distinct from common animal and human pathogens, and thus would not be affected by preexisting immunity in humans and animals. NDV can infect efficiently via the intranasal (IN) route and has been shown to induce humoral and cellular immune responses both at the mucosal and systemic levels in murine and non-human primate models. NDV was used to express protective antigens of simian immunodeficiency virus, respiratory syncytial virus, human immunodeficiency virus in mice; (Nakaya et al., 2004; Martinez-Sobrido et al., 2006).

Recently, recombinant NDV expressing the gD of BoHV-1 has been constructed by Khattar et al (2010). And the vaccine in several aspects including virus replication, pathogenicity for birds, immunogenicity has been investigated. The data suggested that after IN and intratracheal (IT) immunization of calves, the vaccine elicited an immune response against gD and provided partial protection from BoHV-1 challenge. Furthermore, the observation that NDV has a negligible incidence of recombination with other circulating viruses in cattle population makes it a promising and safe vaccine delivery vector candidate for bovine population. So the live viral vector of NDV may be useful for the development of vaccines against foreign animal diseases for which currently safe and effective vaccines are not available.

CONCLUSION

The conventional vaccines were widely used at the early time, but miner effect in reduction of the prevalence of infection was shown. The marker vaccines can be used in companion with virus diagnostic tests to differentiate the infected and vaccinated cattle. European countries are under compulsory or voluntary eradication programs, all involving the application of inactivated or live “marker” vaccines. In the rest of the world, classical attenuated and killed BoHV-1 vaccines are commonly applied. However, the currently used vaccines including inactivated or modified live virus, against BHV-1 have a number of disadvantages. Great effect had been done to develop DNA vaccine with the modification of adjuvant molecules, but little effect was shown to protect the cattle from the virus infection. The Newcastle Disease is a safe delivery vector for non-human primates, but the effect for the control of virus infection in cattle is limited. So the novel strategies must be adopted in the future for the development of effective vaccine with high performance. May be a good adjuvant together with the marker vaccines could result in a good performance in controlling the disease and there remains room for further improvement of BoHV-1 vaccines.

It’s difficult in finding large amount sero-negative bovines, from BoHV-1 free herds, to be used in vaccine potency tests. And the cost for the validation of a vaccine with bovine is much high. Recently, a guinea pig model used for the research in veterinary vaccine of BoHV-1 has been validated (Parreño et al., 2010). This provided a less time consuming and less expensive way in the filed of vaccine research and would contributed to the development of BoHV-1 vaccine.

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