

Control of Bovine Viral Diarrhoea Infections Through Vaccination

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Summary

The main goal of BVDV vaccination is to induce adequate immunity in dams for protecting the infection of foetuses against both genotypes of BVDV-1 and BVDV-2 viruses during pregnancy and thus preventing the establishment of persistent infections as well as preventing severe postnatal infections caused by BVDV-2. The most important problem for BVDV vaccine development is the existence of diversity of BVDV isolates in worldwide. So far, a few BVDV vaccines and vaccination strategies have been given good results for preventing transplacental infections. Live-attenuated BVDV vaccines are better for protection but they have safety concerns. Inactivated vaccines are questionable for inducing adequate broad immune response. There is still a necessity for the development of a better and a novel vaccine for the control of BVDV infections.

Keywords: Bovine viral diarrhoea, Antigenic diversity, Vaccine efficacy and safety, Novel developments

Bovine Viral Diarrhoea Enfeksiyonlarının Aşılama ile Kontrolü

Özet

BVDV enfeksiyonlarına karşı aşılamanın asıl amacı sığırlarda her iki BVDV-1 ve BVDV-2 genotipe ait virüslere koruyucu bağışıklığın oluşması ve gebelik sürecinde fötusun enfeksiyonunun önlenmesi kadar BVDV-2 genotipine ait bazı virüsler tarafından oluşturulan öldürücü enfeksiyonların da önlenmesidir. Günümüze kadar sadece bir kaç aşı ve bazı aşılama stratejileri yüksek oranda başarılı olmuştur. Canlı ve atenüye edilmiş BVDV aşıları daha iyi koruma sağlamakla birlikte, güvenlik sorunları yaratmaktadır. İnaktive aşılarda da geniş spektrumda koruma sağladıkları konusunda tereddütler bulunmaktadır. BVDV kontrolü için halen daha etkili, yeni jenerasyon aşı geliştirilmesine ihtiyaç vardır.

Anahtar sözcükler: Bovine viral diarrhoea, Antijenik çeşitlilik, Aşı etkinliği ve güvenliği, Yeni yaklaşımlar

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INTRODUCTION

Bovine Viral Diarrhoea virus (BVDV) is a member of the genus Pestivirus in the family Flaviviridae. The genus pestivirus official nomenclature currently includes the four accepted species namely; Bovine viral diarrhoea virus-1 BVDV-1, BVDV-2, Classical swine fever virus (CSFV) and Ovine Border disease virus (BDV) and one tentative fifth species isolated from a giraffe¹⁻³.

BVDV is known to be one of the most important pathogens of cattle that causes significant economic losses worldwide⁴⁻⁶. Two genotypes of BVDV have been recognised (BVDV-1 and BVDV-2) based on serological and genetic relatedness⁷⁻¹⁰. Both BVDV-1 and BVDV-2 viruses can exhibit two different biotypes namely, non-cytopathic (ncp) and cytopathic (cp), according to their lytic effect in infected cells.

Both genotypes of BVDV cause a similar range of disease manifestations. These include subclinical or mild infections, enteritis, immunosuppression, foetal infections and persistent infections, haemorrhagic and systemic diseases such as fatal mucosal disease (MD)^{4,11-13}. In addition, certain ncp strains of the BVDV-2 are associated with outbreaks of severe acute haemorrhagic syndrome (HS) characterised by high morbidity and high mortalities were first reported in North America, Canada^{7,8} and recently also detected in Japan and Brazil^{14,15} also in Europe¹⁶⁻¹⁷.

The ncp BVDV infections have the biggest impact if they occur in breeding season or during the pregnancy. The most important outcome of this is the birth of persistently infected (PI) calves. The PI animals that survive are immunotolerant to persisting virus, shed a large amount of virus, and are the key to the spread of BVDV¹⁸⁻¹⁹. These PI animals later develop a deadly MD by superinfection with homologous cp BVDV²⁰. Thus, the rationale of any control measure should be the prevention of intrauterine infection by identifying and eliminating the PI animals and stopping the infection of foetus. The latter can be achieved by immunising animals before pregnancy. Although the identification and elimination of PI animals is the most ideal, vaccination is still the essential control strategy in most countries.

In this review, the protective efficacy of BVDV vaccines and novel BVDV vaccine development studies are discussed.

VACCINATION of CATTLE AGAINST BVDV INFECTIONS

The aim of BVDV vaccination is to give cross protection against common sub-genotypes of BVDV-1 and BVDV-2 to prevent transplacental infections of foetus and thus prevent the establishment of further persistent infections²¹⁻²². Since the emergence of virulent strains of BVDV-2 in Holland through a contaminated vaccine²⁴ and the existence of BVDV-2 isolates in several European countries including UK¹⁸, BVDV-2 may also become threat for other countries in Europe. Therefore, it is also important to protect cattle against severe postnatal infections by BVDV-2.

BVDV vaccines: live attenuated and inactivated

Because of antigenic diversity of both BVDV-1 and BVDV-2, both live-attenuated and inactivated BVDV vaccines containing strains of both genotypes have been developed and in use²⁵⁻²⁷. The live vaccines are based on the attenuated strains and generally induce a broad and long lasting immune response than inactivated vaccines due to the possible involvement of cell-mediated immune response^{28,29}. The inactivated BVDV vaccines are safe and they are formulated in an adjuvant to induce adequate immunity^{30,31}. The duration of immunity induced by inactivated BVDV vaccines tend to be shorter and antibody response against different strains may not be adequate as compared to live vaccines, possibly due to a poor cell-mediated immune response³².

Protective Efficacy of BVDV Vaccines

The main problem for BVDV vaccine development is the existence of diversity of BVDV isolates. BVDV-1 strains were consistently shown to be antigenically distinct from BVDV-2 based on sero-neutralisation assays with polyclonal or monoclonal antibodies^{7,10,15,33-36}.

It was shown that vaccination of cattle with either live-attenuated or inactivated BVDV-1 vaccines was able to induce broad antibody response that neutralised a range of European and American isolates of both BVDV-1 and BVDV-2^{37,38}. This raises the critical question of whether or not cross-reactive immune response elicited by these vaccines could give protection against strains of both genotypes (BVDV-1 and BVDV-2) and subgenotypes within them, particularly BVDV-1a and BVDV-1b.

There have been two good examples for the protective efficacy of two licensed inactivated BVDV vaccines for preventing transplacental infections of bovine foetus. Firstly, a study carried out by Brownlie et al³¹ clearly demonstrated the protective efficacy of the first commercially UK-licensed inactivated vaccine (Bovidec) containing a single ncp strain in all tested cattle for transmitting to challenge virus to their foetus. Secondly, Patel et al³⁹ showed the protective efficacy of an EU-licensed inactivated vaccine (Bovilis) based on a broadly immunogenic cp strain for preventing infection of foetuses against natural BVDV infection for a period of up to six months. Both vaccine strains (Bovidec and Bovilis) belong to BVDV-1a, which is common in England and Wales⁴⁰. However, no data was available for the transplacental protective efficacy of these vaccines against other subgenotypes of BVDV-1 and BVDV-2.

It is suggested that proper vaccination with BVDV-1 vaccines could protect or at least partially protect against BVDV-2 associated clinical disease^{41,42}. Fairbanks et al⁴¹ demonstrated the protective efficacy of a live attenuated BVDV-1a (singer) vaccine against clinical disease in calves challenged with virulent BVDV-2 (890 strain). They observed that BVDV-2 associated clinical disease (e.g. leucopenia and fever) was significantly lower in vaccinated calves as compared to unvaccinated control calves. Makoschey et al⁴² also showed protective efficacy of Bovilis against the clinical effects of BVDV-2 including respiratory disease, leucopenia, diarrhoea with erosions and haemorrhages along the gastro-intestinal tract.

Frey et al⁴³ reported a study showing cross-protective efficacy of a two-step vaccination protocol based on vaccination of dams with an inactivated followed by boosting with a live-attenuated BVDV-1 vaccines against transplacental infections of BVDV-2. Vaccinated dams were challenged intranasally between 30 and 120 days of pregnancy with a mixture of BVDV-1 and BVDV-2. All vaccinated animals gave birth to clinically healthy, seronegative (precolostral) and BVDV-free calves. Dean et al⁴⁴ recently reported the protective efficacy of a live-attenuated vaccine derived from the BVDV-WRL strain belonging to BVDV-1b for preventing infection of foetuses from infection with virulent BVDV-1a strain (7443). In that study, no persistent infection was detected 92% of calves born to dams vaccinated prior to breeding.

Kovacs et al²⁶ showed a good fetal protective effi-

cacy of a commercial multivalent live attenuated BVDV vaccine containing BVDV-1 and BVDV-2 (Breed-Back FP¹⁰, Boehringer Ingelheim Vetmedica Inc.) against challenge of BVDV-1 and BVDV-2. The BVDV components of this vaccine consist of two cp BVDV strains (BVDV-1a singer and BVDV-2 296). Both challenge viruses were heterologous to vaccine strains, highly virulent and well characterised. Vaccination gave protection from foetal infection in 91% of dams challenged with BVDV-1 and in 100% dams challenged with BVDV-2.

Fairbanks et al²⁷ also recently showed a high degree of protective efficacy of a multivalent BVDV vaccine containing the same antigens as Kovacs's. The vaccinated animals prior to breeding were 100% protected against following intranasal challenge with a heterologous BVDV-1 and 95% protected against a heterologous BVDV-2. The challenge viruses were known to induce a high degree of fetal infection and only mild to moderate clinical signs in the dam.

The use of live-attenuated BVDV vaccines containing both genotypes seems to be better for cross protection. However, this strategy can be problematic, since the virus content in these vaccines has been shown to cause transplacental infections and infection of foetuses leading to all outcomes known from natural field infections of BVDV^{28,29}. Furthermore, the use of live-attenuated vaccines may also trigger the induction of MD by RNA recombination with persisting virus^{45,46}.

Vaccination and control of BVDV in Turkey

Several studies have shown that BVDV infections are common in Turkey^{47,48,49}. Burgu et al⁵⁰ reported a recent study based on the examination of BVDV status of nonvaccinated cattle from 26 dairy herds in Turkey. They found that the prevalence of the overall and herd-based persistent infections were 0.07% and 0.61-0.083, respectively. In the same study, BVDV antibody prevalence was ranged from 0.6% to 70.0%.

The control and eradication of BVDV in Turkey can be achieved by identification and elimination of PI animals from herds and immunisation of animals before breeding to prevent infections of foetus which may result in PI calves.

Since BVDV is frequently involved in bovine respiratory disease complex together with infectious bovi-

ne rhinotracheitis virus (IBR), parainfluenza 3 virus (PI-3) and bovine respiratory syncytial virus (BRSV) and other bacterial pathogens⁵¹, BVDV vaccine strains are also included in multivalent vaccines to prevent respiratory disease. In Turkey, there are available multivalent vaccines containing vaccine strains of BVDV-1 and BVDV-2. However, the more deliberate research is necessary to determine genetic and antigenic profile of BVDV isolates circulating in Turkey. This would lead to test protective efficacy of BVDV vaccines by doing vaccination and challenge experiments on target animals.

NOVEL APPROACHES FOR BVDV VACCINE DEVELOPMENT

Although the extensive use of both live-attenuated and inactivated vaccines for controlling BVDV infections, they have important drawbacks and there is still a necessity for the development of a better and novel vaccine for BVDV.

Both DNA and recombinant viral vector or subunit novel BVDV vaccine development strategies have been applied and their protective efficacy tested on an experimental basis.

Recombinant baculovirus E2 protein from BVDV-1a (Singer strain) induced neutralising antibody response in calves and gave limited protection against clinical disease with homologous challenge as evidenced by reduction of viral replication and reduction of fever. However, it failed to protect against heterologous BVDV-2 (890 strain) challenge⁵².

A BVDV-1a DNA vaccine induced neutralising antibody response and cell-mediated immune response in cattle but gave a limited protection against a heterologous BVDV-1b strain⁵³. Nobiron et al⁵⁴ showed the enhancement of the Th1 type immune response in mice by coinjection of BVDV-1a DNA vaccine with IL-2 or GM-CSF DNA. By using same vaccine, the same group later showed a partial protection in cattle that was evidenced by reduced febrile response, reduction of leucopenia and viraemia against the homologous challenge⁵⁵.

Makoschey et al⁵⁶ studied the potential of a 5'NTR deleted stable mutants of a cp strain of BVDV as a live vaccine. These mutants were able to induce high titre neutralising antibody response and gave complete protection of viraemia against challenge with a heterologous BVDV strain.

Liang et al⁵⁷ recently reported an immunisation strategy based on priming with DNA encoding E2 of BVDV-1a (NADL) and boosting with recombinant E2 formulated with CpG oligonucleotides in calves. They showed that all immunised calves developed humoral and cellular immune response which was protective against challenge with BVDV-1b (NY-1).

CONCLUSION

Although the encouraging results were obtained with the novel BVDV vaccines, the protection afforded by them was not complete against a range of BVDV isolates of both genotypes and transplacental infections as compared to current live-attenuated and inactivated BVDV vaccines. There is a basis for their improvement⁵⁸.

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