



Short communication

In vitro neutralization of HoBi-like viruses by antibodies in serum of cattle immunized with inactivated or modified live vaccines of bovine viral diarrhea viruses 1 and 2



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ABSTRACT

HoBi-like viruses are an emerging species of pestiviruses with genetic and antigenic similarities to bovine viral diarrhea viruses 1 and 2 (BVDV1 and BVDV2). Vaccines for HoBi-like viruses are not yet available. However, both modified live virus (MLV) and killed virus (KV) vaccines against BVDV are widely used worldwide. This study evaluated the cross reactive antibody response against HoBi-like pestiviruses in sera of cattle immunized with BVDV1 and BVDV2 vaccines. Groups “KV” and “MLV”, with 25 calves each, received killed or modified live vaccines, respectively, containing both BVDV1 and BVDV2 antigens. The antibody response was evaluated by virus neutralization test. The average of geometric mean titers (GMTs) of neutralizing antibodies in serum against HoBi-like viruses in the MLV group was 12.9, whereas GMTs to BVDV1, BVDV2 and border disease virus (BDV) were 51.1, 23.5, and 12.4, respectively. In this group, neutralizing antibodies against BVDV1, BVDV2, HoBi-like viruses and BDV were detected in 100%, 94%, 68% and 68% of calves, respectively. The GMT of neutralizing antibodies in serum against BVDV1, BVDV2, HoBi-like viruses and BDV in the KV group were 24.7, 14.5, 10.4 and 11, respectively. Similarly, the percentage of animals with neutralizing antibodies against BVDV1, BVDV2, HoBi-like viruses and BDV were 84%, 56%, 34% and 44%, respectively. These results indicate that MLV or killed BVDV1 and BVDV2 vaccines induce a cross reactive antibody response comparatively weak to HoBi-like viruses, and this response would likely not suffice to confer protection.

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1. Introduction

A group of viruses called variously HoBi-like viruses, BVDV3 or atypical pestiviruses, which make up a putative new pestivirus species, have been isolated from FBS (Schirmer et al., 2004) and from natural cases of infection of bovines in several continents (Bauermann et al., 2013). The disease developed by calves infected with HoBi-like strains resembles that historically associated

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with infection by typical virulence BVDV strains (Ridpath et al., 2013).

A variable level of serological cross reactivity among pestiviruses is a well-known phenomenon. Whereas cross reactivity may represent a concern for diagnosis, it suggests some level of cross protection *in vivo*, which is a desirable aspect for immunization strategies. Killed (KV) and modified live (MLV) vaccines are frequently used in BVDV control programs (Ståhl and Alenius, 2011). Compared to KV vaccines, MLV vaccines usually induce higher levels of heterologous protection (Kelling et al., 2007). *In vitro* cross neutralization between BVDV and HoBi-like viruses has been demonstrated (Bauermann et al., 2012; Decaro et al., 2013). While no specific vaccine for HoBi-like viruses is currently available, BVDV vaccines are frequently used in the field. The purpose of the present study is to evaluate the neutralizing antibody response against BVDV1, BVDV2, HoBi-like and BDV pestiviruses developed in cattle immunized with either MLV or KV BVDV vaccines.

2. Materials and methods

Viral strains used in virus neutralizing tests (VNT) were BVDV1 (BVDV1b-NE, BVDV1c-AusB675), BVDV2 (BVDV2a-890, BVDV2a-296nc), HoBi-like (HoBi_D32/00, Italy-1/10-1) and border disease virus (BD31). Border disease virus (BDV), another species in the pestivirus genus that previously was shown to harbor cross reactive epitopes with BVDV (Ridpath et al., 2000), was included for comparison purposes. All viruses were noncytopathic strains and were genotyped based on the 5' UTR.

Sera used in this study were collected from cattle immunized using either an experimental killed (KV) or an experimental modified live virus (MLV) vaccine. Prior to immunization, cattle were tested and found negative for BVDV and antibodies against BVDV. The experimental killed and MLV vaccines used to generate the antisera contained the minimum efficacious dose of antigen needed to generate an immune response and are not reflective of any commercial product. Both the KV and MLV vaccines contain one noncytopathic (NCP) strain of BVDV1, and one strain of BVDV2. Both of these NCP strains were the same in both vaccines. In addition KV vaccine included a cytopathic strain of BVDV1 and an oil base adjuvant. In the KV group, 25 calves, 11 month old, were immunized twice, 28 days apart, with an inactivated vaccine. The MLV group was composed by 25 calves, 5 month old, that received a single dose of a BVDV MLV vaccine. Sera were collected approximately 50 days after the first dose (KV group) or sole vaccination (MLV group). Serum neutralizing antibody titers were measured by VNT as described below. Heterologous noncytopathic viruses were used in VNT and dilution endpoints were determined by immunoperoxidase test (IMPT). Antibody detection was performed as described previously (Bauermann et al., 2012), with minor changes as detailed below. Briefly, twofold dilutions (1:5 to 1:640) of serum samples were run in a triplicate in 96-well plates. The titer of each of the viruses used for VNT was 200 TCID₅₀/

ml, in accordance with the OEI standards (30–421 TCID₅₀/ml). Convalescent sera from animals infected either with a BVDV or a HoBi-like virus were used as positive controls. IMPT was done using a monoclonal antibody (N-2) as described (Ridpath et al., 2000; Bauermann et al., 2012). VNT were calculated and expressed as geometric mean titers (GMTs) using standard methods (Thrusfield, 1986), and the statistical analyses were performed with Friedman–Dunns test using the software GraphPad Prism[®]. Differences were considered significant when the *p* value was below 0.05.

The initial phase of the study used serum from animals immunized with experimental vaccines formulated with minimal efficacious dose. To determine the vaccination response of conventional vaccines delivered to animals raised under production conditions, sera from a third set of calves was evaluated. These calves were vaccinated twice, 20 days apart, with commercially available MLV BVDV vaccine containing strains of BVDV1 and BVDV2 (Bovishield Gold 5[®], Pfizer Animal Health). Twenty days after the second dose (day 40), the serum was collected and submitted to VNT against HoBi_D32/00 and the cytopathic strains of BVDV1 (NADL) and BVDV2 (296c), following the protocol described above.

3. Results

The antibody titers developed by animals in the KV and MLV groups are presented in Fig. 1A. In the KV group, the GMTs were statistically higher (*p* < 0.05) for BVDV1 strains (GMT = 24.7) than to the other pestiviruses tested. While the titers were higher against BVDV2 (GMT = 14.5) than to BDV-BD31 (GMT = 11) and HoBi-like strains (GMT = 10.4), the differences were not statistically significant (*p* < 0.05). Among animals in the MLV group, GMT values for BVDV1, BVDV2, BDV and HoBi-like viruses were, respectively, 51.1, 23.5, 12.4 and 12.9 (Fig. 1A). The average number of animals that developed serum antibodies that neutralized BVDV1, BVDV2, HoBi-like virus and BDV in the KV group was 84%, 56%, 34% and 44%, respectively (Fig. 1B). In the MLV group antibodies were detected in all animals to BVDV1, 94% for BVDV2, 68% for HoBi-like and 68% for BDV (Fig. 1C).

Serum of animals immunized with the commercial vaccine had GMT values of 25, 30.5 and 13.3, respectively, to BVDV1-NADL, BVDV2-296c and HoBi_D32/00. The number of animals with measurable level of neutralizing antibodies in this group was 96% against both BVDV1 and BVDV2 and 60% against HoBi_D32/00.

4. Discussion

These results demonstrate that the antigenic divergence of HoBi-like virus from BVDV1 and BVDV2 is higher than that observed between BVDV1 and BVDV2. Although HoBi-like virus share similarities with BVDV1 and BVDV2 at the glycoprotein E2 (Bauermann et al., 2012), the seroconversion rate against either BVDV species following vaccination with KV or MLV vaccines was 25% higher than the seroconversion rate against HoBi-like virus strains.

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