Vaccine 33 (2015) 422–429

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Early protection in sheep against intratypic heterologous challenge with serotype O foot-and-mouth disease virus using high-potency, emergency vaccine

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ARTICLE INFO

Article history:
Received 5 September 2014
Received in revised form 23 October 2014
Accepted 22 November 2014
Available online 3 December 2014

Keywords:
Foot-and-mouth disease virus
Vaccine efficacy
Heterologous challenge
Sheep

ABSTRACT

In 2009–2011, spread of a serotype O foot-and-mouth disease virus (FMDV) belonging to the South East Asia topotype led to the culling of over 3.5 million cattle and pigs in Japan and Korea. The O1 Manisa vaccine (belonging to the Middle East-South Asian topotype) was used at high potency in Korea to limit the expansion of the outbreak. However, no data are available on the spread of this virus or the efficacy of the O1 Manisa vaccine against this virus in sheep. In this study, the early protection afforded with a high potency (>6 PD_{50}) FMD O1 Manisa vaccine against challenge with the O/SKR/2010 virus was tested in sheep. Sheep ($n=8$) were vaccinated 4 days prior to continuous direct-contact challenge with donor sheep. Donor sheep were infected with FMDV O/SKR/2010 by coronary band inoculation 24 h prior to contact with the vaccinated animals, or unvaccinated controls ($n=4$). Three of the four control sheep became infected, two clinically. All eight O1 Manisa vaccinated sheep were protected from clinical disease. None had detectable antibodies to FMDV non-structural proteins (3ABC), no virus was isolated from nasal swabs, saliva or oro-pharyngeal fluid and none became carriers. Using this model of challenge, sheep were protected against infection as early as 4 days post vaccination.

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1. Introduction

Foot-and-mouth disease (FMD) is a highly infectious disease of cloven-hoofed animals caused by FMD virus (FMDV), a small, positive-sense RNA virus in the Genus *Aphthovirus*, Family *Picornaviridae*. There are seven serotypes of FMDV (O, A, C, Asia 1, SAT 1, SAT 2 and SAT 3) and infection or vaccination with one serotype does not confer protection against the other serotypes [1,2]. Within each serotype are distinct genetic lineages known as topotypes [3]. The genetic variation observed within each serotype can also result in antigenic variation, impairing the ability of vaccines to protect against heterologous strains of the same serotype [4,5]. Serotype O FMDV is the most widespread serotype throughout the world and eight topotypes have been designated [6].

Following the 2001 outbreak in the United Kingdom, deliberation on the necessity of mass culling and the non-vaccination policy led to a re-evaluation of FMD control policies. In both Europe and Australia, emergency vaccination will now be considered in an FMDV outbreak (AUSVETPLAN; EU Council Directive 2003/85/EC) and similar changes are occurring in North America. Understanding the outcome of intratypic (viruses of the same serotype), heterologous challenge for the different vaccine strains is critical when determining which strains should be stored in national antigen banks in case of emergency or used during routine prophylactic vaccination where the latter may still be a part of FMD control. *In vivo* studies remain the most accurate way to determine the effectiveness of FMD vaccines against heterologous challenge (reviewed by [7]).

Sheep represent a large component of the world's FMD-susceptible livestock and some recent outbreaks, including that in the UK in 2001, have involved movement of sheep as an important factor for spreading the infection [8–10]. The clinical signs of FMD in sheep are frequently mild or inapparent, which facilitates the spread of infection due to undetected cases. Furthermore, sheep, like other ruminants, can become long-term sub-clinical carriers of FMDV [11,12] although epidemiologically not important. Vaccination using high potency (>6 protective dose $(PD)_{50}$) vaccines has been shown to be effective in protecting animals challenged as

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http://dx.doi.org/10.1016/j.vaccine.2014.11.043
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early as 4 days post-vaccination (dpv) [13–16], reducing the titre and duration of FMDV excretion, limiting the possibility of transmission and potentially minimising the duration and intensity of an outbreak.

In Australia, FMD is of major concern to the livestock industries, with the potential to cause losses in excess of AUD$50 billion over 10 years [17], as a result of many years of lost revenue due to restrictions placed on the export of Australian products. Foot-and-mouth disease is endemic in many countries in South East Asia (SEA), which through the volume of people and potentially illegal products entering, is considered the most likely source of an FMDV incursion to Australia. In 2009–2011, spread of serotype A and O viruses from SEA led to outbreaks of FMD in six countries in the eastern Asia region [18,19]. Spread of serotype O virus belonging to the SEA topotype led to the culling of over 3.5 million cattle and pigs in Japan and Korea [19]. While the *in vitro* antigenic relationship between the O1 Manisa vaccine (belonging to the ME-SA topotype) and field strains was just acceptable (r value ~0.3), use of this vaccine at high potency in South Korea eventually assisted in controlling the outbreaks [20]. However, no data are available on the spread of this virus or the efficacy of the O1 Manisa vaccine against this virus in sheep.

The current study was undertaken to examine the ability of single vaccination with high potency vaccine (>6 PD_{50}) to afford protection in sheep and prevent the development of persistent infection following heterologous challenge. To mimic an emergency vaccination regime in the field, sheep were vaccinated with O1 Manisa monovalent vaccine and 4 days later challenged by direct contact with sheep infected with the serotype O virus strain that caused outbreaks in South Korea during 2010.

2. Materials and methods

2.1. Ethics statement

This study was performed in strict accordance with the recommendations in the Australian and Canadian codes of practice for the care and use of animals and was endorsed by both the Australian Animal Health Laboratory's Animal Ethics Committee (AEC 1637) and the National Centre for Foreign Animal Disease (NCFAD) Animal Care Committee (C-13-005).

2.2. Animals

Twenty-four Rideau Arcott/Ile de France male sheep aged between 6 and 12 months (~40 kg) were used. All animals were housed in the BSL3 animal facility at the NCFAD, Winnipeg, Canada. The sheep were divided into three groups: unvaccinated, coronary band (CB) inoculated donor sheep (n = 12); vaccinated contact-challenged (VC) sheep (n = 8); and unvaccinated contact-challenged (UC) sheep (n = 4).

2.3. Vaccination

The VC sheep were vaccinated with one full sheep dose (1 ml) of high potency (>6 PD_{50}) FMDV O1 Manisa double-oil emulsion vaccine (Merial Animal Health, Pirbright, UK), administered intramuscularly in the neck region above the left shoulder. Vaccination was given 4 days prior to challenge.

2.4. Challenge

The challenge virus was O/SKR/4/2010 of the SEA topotype (Mya98 lineage), originally isolated from cattle [21], that had been passaged twice in primary bovine thyroid cells (at the FMD World Reference Laboratory, Pirbright Institute, UK) and twice in primary lamb kidney cells (at NCFAD). The P1 capsid coding region of the virus used for inoculation was sequenced and it was confirmed that no known adaptation to cell culture (such as changes to positively charged amino acids mediating binding to heparan sulphate-like moieties) had occurred. The 12 donor sheep were each inoculated intradermally into the CB with 6.5 $\log_{10}$ $TCID_{50}$ of virus in a volume of 0.5 ml. The VC and UC sheep were challenged by direct contact with the donor sheep 24 h later (designated as 0 days post-contact challenge (dpc)). The sheep were arranged into groups of four, housed in separate rooms, with two VC sheep (rooms 1–4) or two UC sheep (rooms 5 and 6) placed in continuous direct contact with two directly inoculated donor sheep.

2.5. Monitoring and sample collection

The sheep were monitored for 35 days after challenge and rectal temperatures and clinical scores were recorded daily to 14 dpc. Sheep showing elevated temperatures (>40.0 °C) were considered as having pyrexia. The tongue, gums and feet were examined for lesions with each site where lesions were observed, not including the inoculation site, given a score of '1′ (maximum score of 5).

Blood, for RT-qPCR and serology, was collected at −4 dpc, daily between −1 and 14 dpc and then weekly to 35 dpc. Nasal secretions, saliva and rectal swabs were collected at the same time points. Swabs were placed in tubes containing 1 ml of phosphate buffered saline for RT-qPCR. Oro-pharyngeal fluid (OPF) was collected with a small probang sampling cup and mixed with 2 ml cell culture media. Collection was at −4, 0, 7, 10 14, 21, 28 and 35 dpc. All samples were stored at −70 °C until processed.

2.6. Virus isolation

Oro-pharyngeal fluid samples were examined for the presence of live virus by inoculation on to foetal bovine kidney (LFBK) cells [22] grown in 24-well cell culture trays, according to standard procedures. Cells were examined for cytopathic effect (CPE) after 24, 48 and 72 h and if no CPE was observed, a blind passage followed. Supernatants were tested using an in-house FMDV antigen enzyme-linked immunosorbent assay (ELISA) [23].

2.7. Detection of FMDV RNA by RT-qPCR

The amount of viral RNA in whole blood, OPF and nasal, oral and faecal swab samples was quantified by a TaqMan RT-qPCR assay [24]. Viral RNA was extracted from 50 μl of sample with the MagMAX™-96 Viral RNA Isolation Kit (Life Technologies) using the MagMAX™ Express-96 Magnetic Particle Processor (Life Technologies). One-step RT-qPCR was performed using the AgPath ID One-Step RT-PCR reagents (Life Technologies) on the Applied Biosystems 7500 Real-Time PCR Instrument. All samples were tested in duplicate and samples with poor Ct value correlation in the duplicate reactions were repeated. Samples with a Ct >36 were considered negative.

2.8. Determination of neutralising antibody titre

Heat inactivated (56 °C, 30 min) serum samples were used for neutralisation assays on LFBK cells. Sera with titres >1.5 $\log_{10}$ (1:32) were considered positive (OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals).

2.9. Detection of antibodies to non-structural and structural proteins by ELISA

Sera were tested for the presence of antibodies against viral non-structural proteins (NSP) by an in-house competitive ELISA

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