Vaccine 33 (2015) 4069–4080

Contents lists available at ScienceDirect

Vaccine

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

Review

Live porcine reproductive and respiratory syndrome virus vaccines: Current status and future direction

Gourapura J. Renukaradhya[a,*], Xiang-Jin Meng[b], Jay G. Calvert[c], Michael Roof[d], Kelly M. Lager[e,**]

[a] Food Animal Health Research Program, Ohio Agricultural Research and Development Center, Department of Veterinary Preventive Medicine, The Ohio State University, Wooster, OH, United States
[b] Department of Biomedical Sciences and Pathobiology, College of Veterinary Medicine, Virginia Polytechnic Institute and State University, Blacksburg, VA, United States
[c] Zoetis, Kalamazoo, MI, United States
[d] Boehringer Ingelheim Vetmedica, Inc., Ames, IA, United States
[e] Virus and Prion Research Unit, National Animal Disease Center, U.S. Department of Agriculture, Ames, IA, United States

ARTICLE INFO

Article history:
Received 31 December 2014
Received in revised form 16 June 2015
Accepted 23 June 2015
Available online 4 July 2015

Keywords:
Porcine reproductive and respiratory syndrome virus (PRRSV)
PRRSV-MLV
Immunity
Cross-protection, Vectors, Infectious cDNA clones

ABSTRACT

Porcine reproductive and respiratory syndrome (PRRS) caused by PRRS virus (PRRSV) was reported in the late 1980s. PRRS still is a huge economic concern to the global pig industry with a current annual loss estimated at one billion US dollars in North America alone. It has been 20 years since the first modified live-attenuated PRRSV vaccine (PRRSV-MLV) became commercially available. PRRSV-MLVs provide homologous protection and help in reducing shedding of heterologous viruses, but they do not completely protect pigs against heterologous field strains. There have been many advances in understanding the biology and ecology of PRRSV; however, the complexities of virus-host interaction and PRRSV vaccinology are not yet completely understood leaving a significant gap for improving breadth of immunity against diverse PRRS isolates. This review provides insights on immunization efforts using infectious PRRSV-based vaccines since the 1990s, beginning with live PRRSV immunization, development and commercialization of PRRSV-MLV, and strategies to overcome the deficiencies of PRRSV-MLV through use of replicating viral vectors expressing multiple PRRSV membrane proteins. Finally, powerful reverse genetics systems (infectious cDNA clones) generated from more than 20 PRRSV isolates of both genotypes 1 and 2 viruses have provided a great resource for exploring many innovative strategies to improve the safety and cross-protective efficacy of live PRRSV vaccines. Examples include vaccines with diminished ability to down-regulate the immune system, positive and negative marker vaccines, multivalent vaccines incorporating antigens from other porcine pathogens, vaccines that carry their own cytokine adjuvants, and chimeric vaccine viruses with the potential for broad cross-protection against heterologous strains. To combat this devastating pig disease in the future, evaluation and commercialization of such improved live PRRSV vaccines is a shared goal among PRRSV researchers, pork producers and biologics companies.

1. Introduction

Porcine reproductive and respiratory syndrome (PRRS) was first described in the late 1980s in the United States, and then in Western Europe in 1990. Hallmark signs of the disease were acute reproductive failure in sows and respiratory disease in pigs of all ages. In 1991, PRRS virus (PRRSV) was discovered in The Netherlands and shown to be the causative agent. This isolate, the Lelystad virus, became the European PRRSV prototype (Type 1) [1]. Soon thereafter, a North American prototype PRRSV, VR-2332 (Type 2), was isolated [2,3]. Each genotype spread rapidly in its respective continent and eventually, both genotypes have been identified in most swine producing regions of the world. Although the Type 1 and Type 2 viruses emerged at about the same time, they are quite genetically diverse having a 40% nucleotide sequence difference between the prototypes, and are quite diverse within a genotype

* Corresponding author. Tel.: +1 330 263 3748; fax: +1 330 263 367.
** Corresponding author. Tel.: +1 515 337 7371; fax: +1 515 337 7149.
E-mail addresses: gourapura.1@osu.edu (G.J. Renukaradhya), kelly.lager@ars.usda.gov (K.M. Lager).

http://dx.doi.org/10.1016/j.vaccine.2015.06.092
0264-410X/

with genetic variation of up to 30% for Type 1 and 21% for Type 2 PRRSV [4,5].

The first commercially available modified live-attenuated PRRSV vaccine (PRRSV-MLV) was released in the United States in 1994, which began a dramatic amount of research into the safety and efficacy of PRRSV-MLV vaccines. The PRRSV-MLV vaccine can induce a protective immune response, but it may not have broad cross-protection against all isolates. Although PRRSV has been eliminated from many swine farms with or without the use of vaccine, frequently these farms re-break with PRRSV indicating a great need for a vaccine that provides broad protection. Moreover, there are concerns about the safety of the PRRSV-MLV for use in naïve pregnant swine and boars demonstrating a similar need for safer, but still efficacious vaccines. There are two general classes of vaccine; one that replicates within the host, and one that does not. This review targets recent advances in vaccine concepts that are replication competent, and the application of these technologies for use in swine.

2. Live PRRSV immunization

The use of a wild-type pathogen as a live vaccine in livestock production is a practice, used when there are no other alternatives to immunize the herd against a disease. In the case of PRRS, this practice of live virus immunization (LVI) has been used to acclimate replacement gilts that would enter into a PRRSV-positive breeding herd. Use of LVI for preventing PRRS in the breeding herd is supported by experimental studies, and practical experience in the field. The practice usually involves infecting young pigs with the endemic virus strain and then collecting blood from them at 3–5 days post-exposure, the presumed peak of virus replication. Serum is harvested from the blood and stored frozen until use as a "vaccine" into replacement gilts. The timing, dose, and frequency of LVI is usually deduced by empirical studies on a farm, thus most LVI practices are tailored to a specific swine production system.

Although the use of LVI has been beneficial, and has been used to eradicate PRRSV from a farm, the practice has many potential risks; *e.g.*, virulent virus may cause severe disease in exposed pigs, quality of the infectious material used for LVI can deteriorate, the LVI inoculum may contain adventitious infectious agents, LVI can perpetuate PRRSV circulation within the herd, and LVI virus may spread virus to adjacent herds [6,7]. Indirectly, LVI virus might predispose animals to secondary bacterial infections due to the inherent properties of wild-type PRRSV to disrupt the pig's immune system. Lastly, the use of LVI has the same issue as other current vaccine strategies, *i.e.*, there can be a lack of cross-protection to field PRRSV isolates.

3. PRRSV-MLV

Commercially available PRRSV-MLV vaccines have been produced by repetitive passage in cell culture under some type of proprietary selective pressure. Most of the cell lines used were derived from the monkey kidney MA-104 cell line, which is the only commonly available continuous cell line that supports replication of PRRSV. However, other cells lines, *e.g.*, MARC-Complimentary cells [8], PK, FK, and BHK cells expressing CD163 [9], PK-15 with CD163 [10], SJPL cells [11], porcine monocytes [12], and ZMAC [13], have been developed and used to propagate PRRSV isolates for vaccine production. Although PRRSV-MLV vaccines around the world have been produced from a variety of field isolates, they have common properties and concerns about use.

The efficacy of PRRSV-MLV vaccines is often described in the label claims as protective against respiratory or reproductive forms of the disease. Some commercial vaccines have licensed the same vaccine across multiple countries and regulatory agencies, and repeatedly demonstrated safety and efficacy against regional wild-type PRRSV isolates. These vaccines may have additional value to global integrated production companies who desire to develop standardized vaccination protocols across systems (regardless of geography), rather than attempting to implement different protocols by region due to differences in vaccine attributes and label claims. Opinions regarding PRRSV-MLV vaccines vary, but they are generally perceived as the most effective and available. Although often noted as having incomplete cross-protection, there are numerous publications reporting protective efficacy against US, EU, and Asian wild type isolates [14–21].

Within the United States, investigators have used PRRSV-MLV based on Type 2 PRRSV and demonstrated significant levels of heterologous protection in both field and laboratory studies across a broad panel of PRRSV field isolates. Benefits of PRRSV-MLV vaccination include reduction of clinical signs, rescue in body weight loss [21], reduced lung lesions [17,22], and reduced viral shedding [23]. Similarly, PRRSV-MLV use and demonstration of heterologous protection is also reported from multiple investigators in Asia. These reports include use of vaccines from North America and local virus derived MLV vaccines to reduce clinical signs and body temperature [24], reduced morbidity, viremia, lung lesions [25–28], and overall health and improved production under field conditions [29]. In Europe the use of PRRSV-MLV vaccines derived from both Type 1 and Type 2 PRRSV is common. A Type 1 virus derived PRRSV-MLV vaccine trial demonstrated reduced clinical and respiratory signs following a heterologous challenge [18]. Following challenge the homologous vaccinates remained virus isolation negative, whereas the heterologous challenged pigs had virus recovered but at a level significantly lower than controls [30]. In contrast, other investigators have reported low levels of protection in a homologous Type 1 PRRSV challenge based on viremia [31]. Type 1 virus derived PRRSV-MLV vaccination administered by intramuscular or intradermal routes followed by a heterologous challenge showed reduced lung lesions with significantly reduced virus isolation titer [19].

PRRSV induced innate, adaptive and immunoregulatory responses at mucosal and systemic sites of infection are delineated in a recent review, which reiterates strategies to enhance the breadth of vaccine-induced immunity by overcoming virus mediated immune evasion [32]. Another review explored reasons behind the limited progress made toward improving the efficacy of PRRSV vaccines [33]. Reasons include uncertainty about viral targets of protective immunity, difficulties understanding the immune correlates of protection, and the vast genetic diversity in PRRSV field isolates. A list of commercially available PRRSV vaccines as of 2011 was provided in an earlier review [33]. In 2012, another PRRSV-MLV vaccine, Fostera™ PRRS (Zoetis), was licensed for use. It is derived from the virulent US field isolate P129 [34] and was attenuated by repeated passage on two cell lines (porcine and hamster origin) that were engineered to express the CD163 PRRSV receptor protein [9]. It is classified as a lineage 8 PRRSV [35], and was evaluated for its ability to cross-protect against a divergent lineage 1 virus from Korea. In spite of sharing only 87.2% nucleotide identity in ORF5, the new vaccine was able to significantly reduce rectal temperature, clinical signs, serum viremia, nasal shedding, and lung lesions [14]. In 2014 Merck Animal Health launched the Prime PAC PRRS+ vaccine, an attenuated form of the Neb-1 (lineage 7) virus.

Since all PRRSV-MLV vaccines replicate in the host, each vaccine virus has the potential for reversion to virulence. Due to this concern, the standard for evaluating the safety profile of PRRSV-MLV vaccines has been elevated by some vaccine regulating agencies which may include increased back passage studies and high-dose safety testing in the most susceptible populations (young pigs and pregnant sows at 90 days of gestation).