Vaccine 33 (2015) 3065–3072

Contents lists available at ScienceDirect

Vaccine

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

Review

Inactivated and subunit vaccines against porcine reproductive and respiratory syndrome: 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] Virology Swine Research Unit, National Animal Disease Center, U.S. Department of Agriculture, Ames, IA, United States

ARTICLE INFO

Article history:
Received 10 February 2015
Received in revised form 18 April 2015
Accepted 30 April 2015
Available online 14 May 2015

Keywords:
Porcine reproductive and respiratory syndrome virus (PRRSV)
Inactivated/killed PRRSV
Immunity
Cross-protection
Delivery system

ABSTRACT

Within a few years of its emergence in the late 1980s, the PRRS virus had spread globally to become the foremost infectious disease concern for the pork industry. Since 1994, modified live-attenuated vaccines against porcine reproductive and respiratory syndrome virus (PRRSV-MLV) have been widely used, but have failed to provide complete protection against emerging and heterologous field strains of the virus. Moreover, like many other MLVs, PRRSV-MLVs have safety concerns including vertical and horizontal transmission of the vaccine virus and several documented incidences of reversion to virulence. Thus, the development of efficacious inactivated vaccines is warranted for the control and eradication of PRRS. Since the early 1990s, researchers have been attempting to develop inactivated PRRSV vaccines, but most of the candidates have failed to elicit protective immunity even against homologous virus challenge. Recent research findings relating to both inactivated and subunit candidate PRRSV vaccines have shown promise, but they need to be pursued further to improve their heterologous efficacy and cost-effectiveness before considering commercialization. In this comprehensive review, we provide information on attempts to develop PRRSV inactivated and subunit vaccines. These includes various virus inactivation strategies, adjuvants, nanoparticle-based vaccine delivery systems, DNA vaccines, and recombinant subunit vaccines produced using baculovirus, plant, and replication-deficient viruses as vector vaccines. Finally, future directions for the development of innovative non-infectious PRRSV vaccines are suggested. Undoubtedly there remains a need for novel PRRSV vaccine strategies targeted to deliver cross-protective, non-infectious vaccines for the control and eradication of PRRS.

1. Introduction

Porcine reproductive and respiratory syndrome (PRRS) is an economically important disease in major pork producing countries causing reproductive failure in sows and respiratory disease in young pigs. Prevention of PRRS in sows is critical to avoid passing PRRS virus (PRRSV) to susceptible pigs through vertical and horizontal transmission resulting in endemic disease and chronic economic loss. PRRSV is an Arterivirus that was discovered almost simultaneously in 1991 on the European and North American continent which lead to the classification of type 1 and 2 PRRSV, respectively. Since the discovery of PRRSV there has been a tremendous growth in the PRRS literature. Genetic studies have revealed this virus to have one of the highest known mutation rates for an RNA virus which promotes extensive antigenic and genetic variation (reported evolutionary rate of $4.7–9.8 \times 10^{-2}$/site/year [1]). Currently, PRRSV consists of at least 9 distinct genetic lineages within type 2 PRRSV, and 3 subtypes within type 1 PRRSV [2,3]. This constant change in the virus is a driving force in the cyclical PRRS epidemics observed in the field, and a major obstacle for developing a broadly-protective vaccine against genetically diverse field

* Corresponding author at: The Ohio State University, FAHRP, OARDC, 1680 Madison Avenue, Wooster 44691, United States. Tel.: +1 330 263 3748; fax: +1 330 263 3677.
** Corresponding author at: Virology Swine Research Unit, National Animal Disease Center, U.S. Department of Agriculture, Ames, IA, United States. 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.2015.04.102
0264-410X/

Table 1
Summary of inactivated PRRSV vaccine studies (2003–2014).

Vaccine and dose	Route/no. of doses	Pigs age	PRRSV chal. and route	Adjuvant	Viremia	Viral load in lungs	VN titer (log_2)	IFNγ ELISPOT	Cell proliferation	Citations
Promise (type 2)	IM/2	8 wks	–	+	–		<2	<50 spots	–	2003 [83]
Promise (type 2)	IM/6	Sows	–	+	–	–	>3	–	++	2004 [19]
Promise (type 1)	IM/2	10 wks	–	+	↔	–	>4	<100 spots	–	2004 [16]
Progressis (type 1)	IM/2	~6 wks	+ IN homologous	+	–	–	–	>300 spots	–	2005 [18]
Progressis (type 1)	IM/2	6–8 wks	–	+	–	–	–	> 300 spots	–	2005 [18]
Progressis (type 1)	IM/5	Gilts Sows	–	+	–	–	Improved reproductive performance	2006 [14]		
Lelystad–1×10^8 $TCID_{50}$	BPL-killed IM/2	6 wks	+ IN homologous	w/o emulsion	1 log_{10} ↓	–	>3	–	–	2006 [23]
Suvaxyn (type 1)	IM/2	Gilts	+ IN homologous	+	2 log_{10}↓ on day 9	–	>5	Preweaning mortality↓	2007 [17]	
Progressis (type 1)	IM/2	20 wks	+ IN homologous	+	↔	↔	>5	>100 spots	–	2007 [15]
Lelystad -0.5×10^6	Killed IN/2	4 wks	–	CpG–10,100, 1000 μg	–	–	–	IFNγ in culture sup ↑	+++	2007 [84]
Killed vac (China)	IM/2	4 wks	+ IN homologous	+	↔	–	>4	–	+	2007 [85]
Lelystad–1×10^8	BEI-killed IM/2	6 wks	+ IN homologous	IFA	2 log_{10} ↓	–	>3	–	–	2009 [10]
Lelystad–1×10^8	BEI-killed IM/2	6 wks	+ IN Homologous	Alhydrogel	2 log_{10} ↓	–	>2	–	–	2009 [10]
Lelystad–1×10^8	BEI killed IM/2	6 wks	+ IN homologous	Suvaxyn o/w	2 log_{10} ↓	–	>4	–	–	2009 [10]
07V063–1×10^8	BEI-killed IM/2	Gilts	+ IN homologous	Suvaxyn o/w	Early clearance	–	>3	–	–	2012 [24]
VR2332 2.5×10^6	UV-killed nanoparticle -IN/1	6 wks	+ IN heterologous (MN184)*	None	2 log_{10}↓ Early clearance	–	>3	IFNγ in culture sup ↑	–	2012 [20]
VR2332 2.5×10^6	UV-killed nanoparticle -IN/1	6 wks	+ IN homologous	None	2 log_{10}↓ early clearance	–	>3	IFNγ in culture sup ↑	–	2013 [21]
VR2332 2.5×10^6	UV-killed nanoparticle -IN/2	6 wks	+ IN heterologous (MN184)*	*M.tb* WCL	4 log_{10}↓ RNA & Neg - virus isolation	6 log_{10}↓ RNA & Neg - virus isolation	>4 in serum & ~5 in lungs	>1000 spots & IFNγ$^+$ cells↑	++++	2014 [22,40]
FL12/GP5 DM virus 1×10^8	BEI-killed IM/2	3 wks	+ IM homologous	Montanide	2 log_{10}↓	–	4	–	–	2014 [86]

Notes: IN—intranasal; IM—intramuscular; ID—intradermal; wks—weeks; virus titers in $TCID_{50}$—tissue culture infective dose 50: Homologous—genetically identical PRRSV strain; Heterologous – genetically partially different PRRSV strain; '–'—negative/none/nil; '+'—positive; + weak; ++ mild; +++ high; ++++ very high. Commercial vaccines: Promise (Bayer); Progressis (Merial); Suvaxyn (FortDodge). * PRRSV strains VR2332 and MN184 are 10–16% genetically different in ORF 2 to 5 sequences [87].