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Combination of Adt-O1Manisa and Ad5-boIFNλ3 induces early protective immunity against foot-and-mouth disease in cattle

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ABSTRACT

Foot-and-mouth-disease (FMD) remains the most infectious livestock disease worldwide. Although commercially available inactivated or adenovirus-vectored-vaccines (Ad5-FMD) are effective, they require 5–7 days to induce protection. Therefore, new control strategies that stimulate rapid immune responses are needed. Expression of bovine interferon λ3 using the Ad5-vector platform (Ad5-boIFNλ3) is able to delay disease in cattle, but clinical signs appear at 9 days after challenge. We hypothesized that combination of Ad5-boIFNλ3 and Ad5-FMD could induce immediate and lasting protection against FMD. Cattle were vaccinated with an Ad5-FMD, Ad5-boIFNλ3, or the combination of both, followed by challenge at three days post-immunization. All animals treated with Ad5-FMD combined with Ad5-boIFNλ3 were fully protected against FMD, despite the absence of systemic neutralizing antibodies or antiviral activity at the time of challenge. Induction of a strong cell-mediated immune response suggested that Ad5-boIFNλ3 is able to act as an adjuvant of Ad5-FMD vaccine in cattle.

1. Introduction

Foot-and-mouth-disease (FMD) is one of the most important viral-diseases that can affect livestock worldwide. The etiological agent is the FMD virus (FMDV), a positive-sense single-stranded RNA virus belonging to the *Aphthovirus* genus of the Picornaviridae family. FMDV is characterized by a high replication rate, resulting in short disease-incubation time, high levels of virus excretion via aerosol, and high level of contagiousness within exposed susceptible animals since practically all exposed animals get sick. The virus is antigenically variable, as displayed by 7 serotypes (A, O, C, Asia 1, and South African Territories 1, 2, and 3) and multiple subtypes (Domingo et al., 2003; Grubman and Baxt, 2004). Although FMD results in high morbidity, mortality is low, except in young animals that can develop cardiac complications (Alexandersen et al., 2003). Infected animals usually develop vesicular lesions on the tongue, mouth, feet and teats, and as a result, animal production is diminished. Although the disease has been successfully controlled in many geographic regions, mainly due to the enforcement of surveillance and trading policies and the use of a commercially available inactivated whole virus vaccine formulation, challenges remain as outbreaks are frequently detected in most of the developing world. Importantly, enforcement of international policy limits the trading of FMD-susceptible animals or derived products from countries in which the disease is present (OIE, 2012). Thus, the presence of FMD may have catastrophic economic consequences for the affected countries. The current approved chemically inactivated whole virus vaccine that induces a $CD4^+$ T cell-dependent humoral response (Carr et al., 2013) has several limitations: i) it requires approximately 7 days to induce protection; ii) it requires expensive high containment facilities for production; iii) it is not genetically stable since repeated passage in tissue culture is needed to achieve high titers thus increasing the probability of selection of antigenic variants, iv) it does not confer long term protection thus requiring semiannual vaccination; v) depending on the purification protocol, vaccine contamination with viral non-structural (NS) proteins could affect the ability to differentiate infected from vaccinated animals (DIVA capability) (Doel, 2003). An alternative vaccine approach that overcomes most of the limitations of the inactivated FMD vaccine consists of a live recombinant replication-defective human adenovirus type 5 (Ad5) vector expressing FMDV antigens (Ad5-FMD). The Ad5-FMD vaccine delivers FMDV empty capsids since it only codes for all the structural but only a few NS viral proteins required for optimal capsid expression,

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processing and assembly, thus allowing for DIVA and avoiding the necessity of expensive high-containment manufacturing facilities (Mayr et al., 2001; Grubman et al., 2010). Interestingly, this vaccine has been industrially developed and, for the first time in the last 50 years, it received a provisional U.S. license for production and use in the U.S mainland in emergency situations (Grubman et al., 2010). The Ad5-FMD vaccine not only induces a protective neutralizing antibody response, but also a significant antigen specific-$CD4^+$ and $CD8^+$ T cell response (Moraes et al., 2011). However, neither this live Ad5-vectored nor the inactivated FMD-vaccines are able to confer complete protection prior to 7 days post-vaccination (dpv). More recently, protection of cattle vaccinated with the inactivated whole FMDV vaccine formulated with a new adjuvant has been reported as early as 4 dpv (Quattrocchi et al., 2014). However, 4 days still allows a window of opportunity for the virus to replicate and rapidly spread. In an effort to address this deficiency, we have previously shown that treatment with Ad5 that express type I, type II or type III interferons (IFNs) can fully protect swine against challenge with multiple FMDV serotypes early after treatment (1-3 days post-treatment) (Chinsangaram et al., 2003; Moraes et al., 2003; 2007; Dias et al., 2011; Perez-Martin et al., 2014). In particular, type I IFN (e.g. IFNα) protection was correlated with recruitment of dendritic cells (DCs) to the skin (Diaz-San Segundo et al., 2010), which showed a partial maturation phenotype with increased expression of CD80/86, and decreased phagocytic activity (Diaz-San Segundo et al., 2013). In the case of cattle, thus far the most successful approach using IFNs has been achieved with type III IFN expressed by the Ad5 vector (Ad5-boIFNλ3). However, although Ad5-boIFNλ3 was able to delay disease onset in cattle, some animals showed clinical signs starting 9 days after challenge (Perez-Martin et al., 2012).

Type III IFN is a relatively recently identified class of IFN with antiviral properties similar to type I IFN (α/β) that is present in several animal species including humans, mice, swine, chickens and bovines (Kotenko et al., 2003; Karpala et al., 2008; Sheppard et al., 2003; Sommereyns et al., 2008; Sang et al., 2010; Diaz-San Segundo et al., 2011). The type III family consists of three members, IFNλ1, λ2 and λ3, which are also known as interleukin (IL)-29, IL-28A and IL-28B, respectively. A fourth member of the IFNλ family has been described in a sub-fraction of the human population (Prokunina-Olsson et al., 2013). Compared with type I IFN, type III IFN stimulates similar innate antiviral responses through activation of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway to induce IFN stimulated gene (ISG) expression (Zhou et al., 2007). However, IFNλ signals through a different receptor, a heterodimer of two subunits, IL-28B receptor alpha (IL-28Rα) and IL-10Rβ, the last shared by the IL-10 family of cytokines (Kotenko et al., 2003; Sheppard

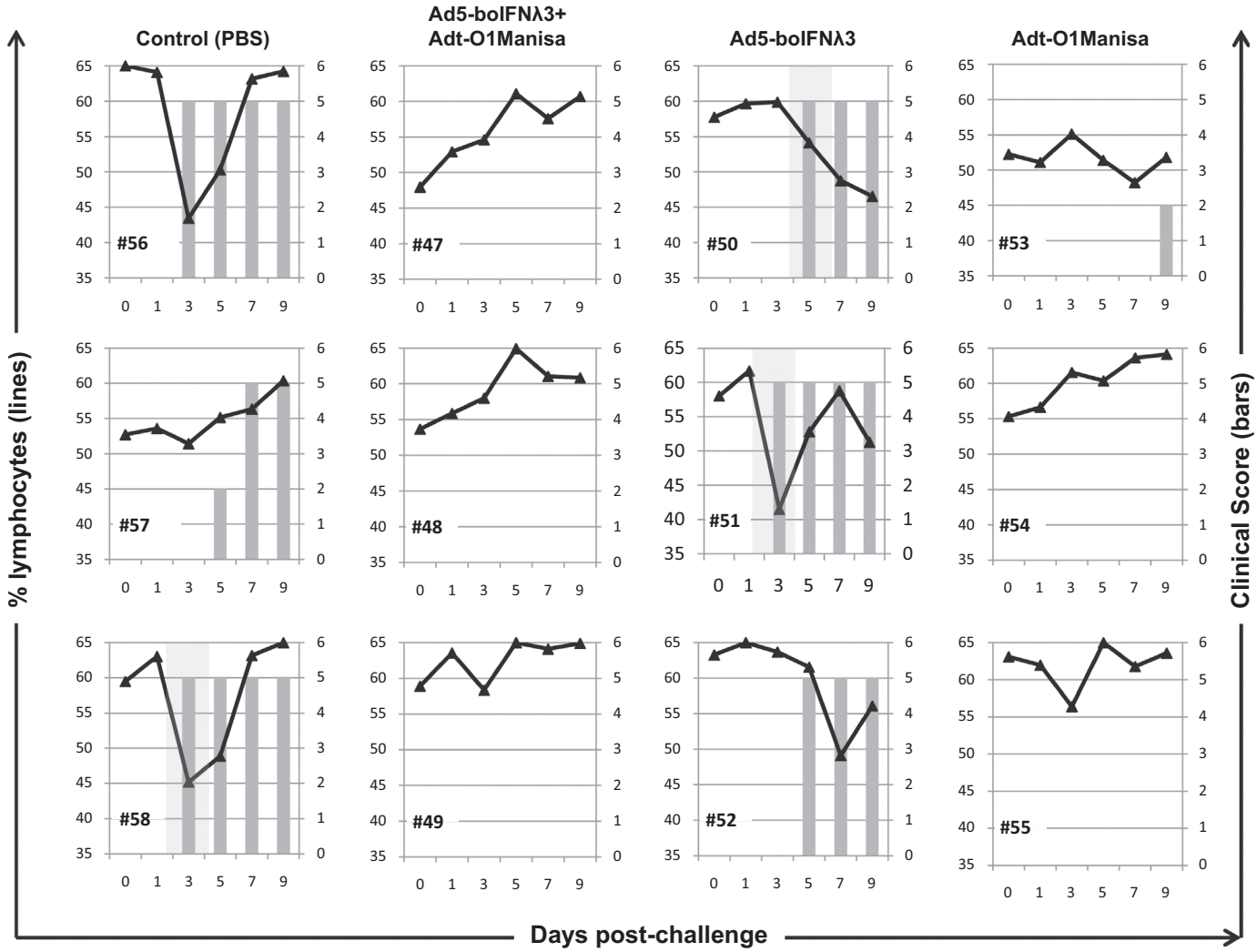

Fig. 1. Clinical outcome after challenge with FMDV O1Manisa. Clinical signs (bars), temperature (shaded area) and lymphopenia (lines) were evaluated during the first week after challenge and represented for each animal individually. Clinical score is expressed as number of feet showing lesions plus one more point scored when lesions were present in the tongue, nostrils and/or lips (maximum score is 5). Lymphocytes in blood are represented as percentage. Shaded area represents the days after challenge when the animals had high temperature (> 40°C).