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Review paper

A systematic review of the immune-modulators *Parapoxvirus ovis* and *Propionibacterium acnes* for the prevention of respiratory disease and other infections in the horse

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ABSTRACT

Inactivated *Parapoxvirus ovis* (iPPVO) and *Propionibacterium acnes* (*P. acnes*) are currently used in equine medicine as immune-modulators for prophylactic treatment or adjunct to conventional therapy in order to improve immune defences, to prevent or treat infectious diseases. Their mode of action relies on a non-antigen specific interaction with the innate and/or adaptive immune responses. iPPVO stimulates and regulates cytokine secretion by leucocytes, while *P. acnes* acts primarily through the activation of macrophages. This report aims to describe their activity as immune-modulators and to summarise the scientific literature and reports available about their use in horses, particularly in the prevention or treatment of equine respiratory diseases. This systematic review regroups articles published in peer-review journals, clinical trials reports, conference proceedings and other information made available in the last 2 decades.

Contents

1. Innate immunity to respiratory infection and principle of immune-modulation

The equine respiratory disease complex (ERDC) is a term used to regroup a set of common equine viruses such as equine herpesvirus type 1 and 4 (EHV-1/4), equine influenza virus (EIV), equine arteritis virus (EAV) or equine adenovirus (Landolt et al., 2007; Slater, 2007a,b).[1] These respiratory viruses all primarily induce an indistinguishable respiratory disease in horses, characterised by pyrexia, cough and nasal discharge. Depending on the causative

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[1] Respiratory Diseases of Horses: Introduction – The Merck Veterinary Manual. 2011. http://www.merckvetmanual.com/mvm/index.jsp?cfile=htm/bc/121300.htm.

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pathogen, specific secondary pathology may occur (*e.g.* EHV-1 abortion or myeloencephalopathy). Occasionally, ERDC is complicated by secondary bacterial infection mostly caused by *Streptococcus equi* spp *zooepidemicus*, an opportunistic pathogen of the respiratory tract. *Streptococcus equi* spp *equi* (*S. equi*) and *Rhodococcus equi* (*R. equi*) are other important primary respiratory bacterial pathogens, causative agents of Strangles and pneumonia in young foals, respectively (Giguere et al., 2011; Waller et al., 2011).

Vaccination is essential to prevent or limit the development of ERDC associated respiratory diseases and/or bacterial infections. Regrettably, protection induced by vaccination is not always optimal. In absence of pre-existing immunity induced by vaccination, maternal derived antibody or natural exposure to the pathogen, the mucosal innate immunity represents an essential line of defence of the horse. Its role is to contain the infection until the pathogen-specific adaptive immune response has been stimulated. Innate immunity starts with an immediate response composed of preformed factors (*e.g.* complement proteins) and resident mononuclear cells (*e.g.* macrophages, dendritic cells (DC) (Kohlmeier and Woodland, 2009; Shishido et al., 2012)). Alveolar macrophages are predominant in the lumen of the respiratory tract and in broncho-alveolar lavage (BAL) fluids of horses (Flaminio et al., 1998; Hoffman, 2008). The primary activity of macrophages is to destroy pathogens. Alongside DC, macrophages also act as professional antigen presenting cells (APC) by recognising invading-pathogens through their pattern-recognition receptors (PRRs), which is essential for the development of both innate and adaptive immune responses (Iwasaki and Medzhitov, 2004; Kohlmeier and Woodland, 2009). Their last important function is synthesis of pro-inflammatory cytokines including interleukins (IL-1, IL-6, IL-8, IL-12) and tumour necrosis factor alpha (TNF alpha) along with mediators that recruit new phagocytic cells to local sites of infection. The combination of IL-1, IL-6 and TNF alpha (also called endogenous pyrogens) will cause a rise in body temperature. Other cytokines (*e.g.* Type I Interferon; IFN alpha and beta) are also rapidly synthesised by both virus-infected cells and cells of innate immunity (*e.g.* macrophages, plasmacytoid cells and DC), during the early phase of infection (Kohlmeier and Woodland, 2009). Interferon and IL-6 synthesis were measured in horses after EHV-1 or EIV infection (Edington et al., 1989; Wattrang et al., 2003). These molecules present a wide range of antiviral activities, inducing up-regulation of major histocompatibility complex (MHC) class I molecules and antiviral resistance in uninfected cells. These cytokines compose the inducible phase of the innate response and play an essential role in stimulation of natural killer (NK) cells that are an early defence against intracellular infections. NK cells are activated by IFN alpha and IL-12 synthesised by macrophages, and are cytotoxic for virus-infected cells with absent or abnormally low levels of MHC class I expression (a means of immune evasion to avoid recognition by cytotoxic T-lymphocytes). Cytokines and chemokines locally produced during the infection are also essential for the maturation and the trafficking of DCs to draining lymph nodes where the adaptive immune response will be initiated (Kohlmeier and Woodland, 2009). IFN gamma synthesised by NK cells (He et al., 2004) will drive the development of a T-helper 1 (Th1) adaptive immune response, most effective against intracellular pathogens (Boehm et al., 1997). Modification of the cytokine balance initiated during the innate response may have a deep impact on subsequent development of T helper cells, T regulatory cells and cytotoxic lymphocytes responses, all major actors of the adaptive immunity (Fig. 1).

Nonspecific immune-modulators are molecules that interact with the innate and/or adaptive immune response but are not specific to an antigen. Their activity is based on the activation of innate cells and subsequent cytokine production (Rush and Flaminio, 2000). Through their ability to increase immune competence (activation, suppression and/or regulation), immune-modulators have a role to play to achieve or improve protection against infection, and to support animals whose immune function and response are sub-optimal, impaired/suppressed or dysregulated. Immune-modulator products have been used for years in veterinary medicine. *Parapoxvirus ovis* (PPVO) and *Propionibacterium acnes* (*P. acnes*) are 2 immune-modulators commercially available for the treatment of dogs, cats, horses and cattles. This review aims to summarise the scientific literature currently available on their use in horses.

2. Methods

This systematic review regroups articles published in peer-review journals and clinical trials reports, which characterise PPVO and/or *P. acnes* activity *in vitro* and their use *in vivo* in horses. Due to the limited amount of scientific literature available on this subject, conference proceedings, manufacturing reports, round-table discussions, reviews and abstracts were also considered. The language of publication is mostly English, but not exclusive. Publication date ranged from 1980s to the present time. Studies and reports were identified by searching electronic databases (Pubmed/Medline, Scopus and GoogleScholar) and scanning reference lists of articles/reports (Fig. 2). The PRISMA (Preferred Reporting Items for Systematic reviews) guidelines were consulted for the preparation of this review (Moher et al., 2009). The last search was run in September 2012. Information was extracted from each included study and report on context of the study (*e.g.* pathogen), type of intervention (dose, duration and frequency), number of participants in each group and type of outcome (specific to the pathogen targeted). Details of the search strategy are presented in supplementary data 1 (Table 1).

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vetimm.2013.01.010.

3. Immune-modulators used in horses

3.1. *Parapoxvirus ovis*

PPVO (Orf virus) belongs to the poxvirus family. PPVO is a host restricted DNA virus that primarily induces skin lesions in sheep and goats and is transmissible to humans (Haig and Mercer, 1998). One strategy used by poxviruses