Immunization against Paratuberculosis - Current Perspectives

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Abstract

Johne’s disease is chronic progressive enteritis of domestic and wild ruminants caused by Mycobacterium avium subsp. paratuberculosis. Organism is very sturdy in environment and young animals are more susceptible to the disease from infected carriers via contaminated milk, feed and colostrums. For the dairy industry, economic losses from Johne’s disease are primarily due to premature disposal of animals and reduced milk production. Therefore, a vaccine that prevents animals from becoming infected would be an ideal goal and there is no proper test for the diagnosis, it is prudent to control the disease by immunization. There are mainly three types of vaccine, which are killed, modified live and subunit vaccine. Current vaccines could reduce the severity of infections but they are all failing to give sterile and long lasting immunity. So it is imperative that experimental studies should be conducted to produce an ideal vaccine candidate against MAP.

Key words: Paratuberculosis, Immunization, Killed Vaccine, Live Vaccine, Subunit Vaccine

Introduction

Mycobacterium avium subsp. paratuberculosis (MAP) is the causative agent of Johne’s disease or paratuberculosis. Paratuberculosis described first in 1895 by Johne and Frothingam has been considered a major disease of ruminant population for over a century. The disease has an increasing economic impact worldwide and its zoonotic relevance in association with Crohn’s disease in human has been described (Pradhan et al., 2011). It is primarily considered as a disease of domesticated and wild ruminants. But most recently, the natural disease has been reported in rabbits, hare, and in a number of other wildlife species. In cattle, disease is characterized by gradual weight loss, decreased milk production and diarrhea due to chronic, progressive, granulomatous enteritis and lymphadenitis (Chiodini et al, 1984).
MAP infections are usually acquired during calf hood via the ingestion of contaminated colostrum, milk, feed and water, and fecal shedding of organisms by infected cattle usually starts around 2 years of age (Sweeny, 1996). Reportedly, the prevalence of MAP infection in US dairy herds ranges from 20 to 40% and costs to the dairy industry are estimated at $220 million annually. In addition to the direct losses, the need for premature culling of MAP-infected animals reduces the herd manager’s ability to cull for other health-related problems and low productivity in terms of weight loss and milk yield. Johne’s disease is endemic in developing and developed countries (Abbas et al., 2011).

The control and eradication of Johne’s disease has been mainly hampered by the non-availability of suitable methods that can detect animals in early stages of infection. Paratuberculosis is difficult to diagnose in animals that have no clinical signs. Clinical signs of the disease do not typically develop for several years after initial infection because of the slow growing nature of the organism and the change to humoral immunity from cell-mediated immunity during the late stage of infection. At this stage of infection, organisms may be present in the faeces in insufficient numbers to be detected by current culture methods. In addition, animals in the early stages of infection often do not elicit an immune response that is detectable by current tests.

Need for Vaccination for Johne’s Disease

In endemic areas, animals are exposed daily to MAP from the contaminated environment, but animals younger than 6 months, with a functionally immature immune system, are particularly susceptible to MAP (Larsen et al., 1975) and will become infected during the first months of life by ingestion of contaminated colostrum, milk, water and feed (Sweeney, 1996). The immune system of the newborn has a strong tendency to adopt a Th2-type profile, whereas a Th1-type profile is thought to be essential for protection against intracellular pathogens, such as mycobacteria. Vaccination of dams may represent an alternative approach in the control of infection of newborns.

Johne’s Disease Vaccines

Vaccination against MAP was first reported in 1926 by Vallée and Rinjard. Their vaccine consisted of a live non-virulent strain of MAP adjuvanted in a mix of olive oil, liquid paraffin and pumice powder. Now days, a number of live-attenuated and killed whole-cell-based vaccines were developed both for bovine and ovine Johne’s disease which are suspended in mineral oil, are inoculated subcutaneously in cattle within 30 days of birth in the brisket (Bakker et al., 2000). In goats, sheep and deer, vaccines are generally injected in the neck behind the ear (Gilmour, 1976).

Types of Vaccines

A. Killed whole-cell-based vaccines
Mycopar is a commercial vaccine in USA developed from Strain 18 and is actually composed of killed *M. avium* subsp. *avium* helps in increasing antibody response against MAP and prevented further infection but causes interference in ELISA results (Chiodini, 1993; Spangler *et al.*, 1991). “Lelystad” vaccine, manufactured in Netherlands, is composed of heat-killed MAP bacteria suspended in a water-oil emulsion and “Gudair” vaccine from strain 316 F developed in Spain are found to increase IFN-γ production (Corpa *et al.*, 2000; Reddacliff *et al.*, 2006). Bergey strain is an experimental vaccine developed in Hungary, composed of a heat-killed MAP but it gives erroneous results in delayed hypersensitivity test with purified protein derivative (Kormendy, 1994). Killed commercial vaccine Strain 18 killed MAP field-isolate adjuvanted with human IL-12 induced strong local, systemic and enteric IFN-γ responses. (Park and Scott, 2001). “Silirum” is a killed vaccine composed of MAP strain 316F combined with highly refined mineral oils to reduces the granuloma formation and interference with Johnin test (Munoz *et al.*, 2005). All these heat killed vaccines are given at less than 1 month of age. An indigenous killed vaccine developed using “Indian bison type” genotype of Mycobacterium avium subspecies paratuberculosis Strain “S5” of Goat Origin had been found out to be an effective therapeutic and preventive vaccine against small ruminant paratuberculosis (Singh *et al* 2013).

**B. Live-attenuated Whole Cell Based Vaccines**

“Neoparase”, oil adjuvanted, freeze-dried live modified 316 F strain is a therapeutic, post exposure vaccine but interferes with Johnin test (Gwozdz *et al.*, 2000). “Paratuberkulose vaksine”, is based on two British reference strains of MAP (2E and 316F) adjuvanted in a mix of olive oil, liquid paraffin and pumice powder (Saxegaard and Fodstad 1985). These vaccines are administered after 1 year of age. “AquaVax” is an aqueous suspension of live MAP strain 316F and induces low transient immune responses (Begg and Griffin, 2005). Cell wall competent or spheroplast MAP vaccines adjuvanted in either alum or saponin were not having significant effect on fecal shedding, but saponin had less systemic side effects and were having weak interference with comparative skin tests than vaccines adjuvanted with alum. (Hines *et al.*, 2007)

All these whole-cell-based vaccines, particularly oil adjuvant ones interfere with the existing diagnostic tests for bovine tuberculosis as they induce a positive in vitro IFN-γ response and interfere with the existing sero-diagnostic tests for paratuberculosis and these are not really characterized with respect to their attenuation (Emery and Whittington, 2004).

**C. Subunit Based Vaccines**

The three members of the Ag85 complex are highly conserved proteins with mycolyl-transferase activity present in all mycobacterial species and abundantly secreted in mycobacterial culture filtrate. The Ag85A and Ag85B components of *M. tuberculosis* are among the most promising vaccine candidates for human
tuberculosis (Andersen et al., 2004). Strong T-cell responses can be detected against Ag85 complex in low and medium shedder animals, but not in culture-negative cows (Shin et al., 2005). Heat-shock protein (Hsp) 65 (GroEL) and Hsp70 (DnaK) can also induce specific immune responses in MAP-infected and MAP-vaccinated cattle. As for PPD responses, the mycobacterial Hsp70-specific CMI responses decrease upon progression to the clinical stage of the disease (Koets et al., 1999).

P22 is an MAP protein belonging to the LppX/LprAFG family of putative mycobacterial lipoproteins induces good IFN-γ and antibody (Rigden et al., 2006). Another lipoprotein, the 19-kDa (MAP0261c) protein stimulates strong humoral but weak IFN-γ production in infected cattle (Huntley et al., 2005). Superoxide dismutase (SOD) is a 23-kDa intracellular protein which strongly induces γ δ+ T cells in cattle (Shin et al., 2005). Alkyl hydroperoxide reductases C (AhpC) and D (AhpD) are constitutively expressed by MAP in vitro and homologous antigens elicited a strong IFN-γ response (Olsen et al., 2000).

D. DNA Vaccines and Heterologus Vaccines

DNA vaccines induce strong CD4+ and CD8+ mediated immune responses in mice. MAP is an intracellular pathogen, therefore, cell mediated immunity plays a key role in the control of the bacterial replication and the subsequent protection against paratuberculosis. High, antigen-specific pre-challenge spleen cell IFN-γ levels often correlate with the best protection. Secreted and surface-exposed cell wall proteins are major antigens recognized by the protective immune response against MAP infection (Anderson et al., 2004).

DNA vaccines encoding Ag 85A, Ag 85B and SOD could induce significant lymphocyte proliferation as well as the secretion of Th1-associated cytokines including interferon gamma (IFN-γ), interleukin-2 (IL-2), IL-12, and tumor necrosis factor alpha (Shin et al 2005 Immunization with a DNA vaccine cocktail induces a Th1 response and protects mice against MAP challenge. Attenuated Salmonella expressing MAP antigens has emerged as a promising vaccine candidate which protect against both MAP and salmonella infection and has important implication in developing a marker vaccine which could overcome the major limitation of current vaccines used in the field (Chandra et al 2012).

Conclusion

An ideal vaccine against paratuberculosis or Johne’s disease should provide sterile immunity, or abolish faecal shedding. The vaccines currently available reduce clinical symptoms but cannot avoid the contamination due to fecal shedding. A better understanding of the molecular and immunological processes involved in the progression to clinical paratuberculosis may help to develop more efficient vaccines. Finally, the development of subunit vaccines will require the further identification and discrimination of MAP antigens with either a strong immunodiagnostic potential. New experimental infection models to test vaccine efficacy are needed. Evaluation of the new vaccines should use
experimental challenge conditions with dose and inoculation route similar to natural infection. Due to the slow progression of the disease, a compromise must be found between the length of the follow-up to validate a potential protective efficacy and the cost-management involved in this study.

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