Rhodococcus equi plasma and the equine neonate

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Introduction

Rhodococcus (Corynebacterium) equi was initially described by Magnusson (1) as a causative agent of primarily purulent pneumonia in foals and represents a serious risk worldwide accounting for greater than 3% of foals deaths. The disease affects foals, usually less than six months old, causing a suppurative bronchopneumonia and lymphadenitis. A decline in maternal antibodies coincides with the typical age of onset of R.equi infection in foals, thereby providing some evidence for a role of antibodies in protecting against R.equi disease. This is the basis for considering administration of plasma (such as HYPERMUNE-RE) containing specific antibodies as part of an overall preventive management strategy on endemic stud farms. This has prompted many authors to report apparent success using plasma in reducing foal morbidity and mortality (2, 3, 4, 7, 8), particularly as recent attempts to develop a protective vaccine have failed (9, 10).

“effective immunoprophylaxis can be achieved by administering plasma containing specific antibody”

The discovery of virulence associated antigens and plasmids have allowed the virulence of R.equi strains to be classified. The surface expressed Virulence Associated Protein A (VapA) has been shown to be an essential virulence factor of R.equi (13), and therefore only strains that contain this protein are considered capable of causing disease. It has also been demonstrated that the effective specific antibody is likely to be against VapA (14, 15), and therefore important for opsonisation of the bacterium. Consequently, Veterinary Immunogenics Ltd uses a vaccine, comprising European strains of virulent R.equi, specially made for use in its donor horses which stimulates antibodies to the VapA protein as well as to other specific R.equi antigens. The application of assays in both this company and in an independent laboratory in California of the plasma subsequently harvested, HYPERMUNE-RE, showed strong reaction to VapA proteins and demonstrated a measurable potency of titres. In addition, research in England (5) has demonstrated antibody present in HYPERMUNE-RE to another R.equi cell

envelope component, lipoarabinomannan (LAM). This may provide additional benefit in reducing the immunosuppressive effect of the bacterium in the foal lung by allowing white cell function. A recent review of R.equi disease (11) has been published and provides a more detailed account of the pathogenesis of the bacterium including virulence mechanisms, which has been greatly facilitated by the recent R.equi genome project (12).

Developments

In 2003 Veterinary Immunogenics Ltd (Veterinary Immunogenics) formed a joint initiative with a scientific team with expertise in immunology, microbiology and molecular biology. The subsequent programme of research resulted in a greater understanding of the immunological characteristics of R.equi and the development and validation of two ELISA tests for measuring firstly general R.equi antibodies, and secondly specific VapA antibodies. This research has gathered significant information relating to the R.equi vaccine used in the donor horses, enhancement of the key specific antibodies in HYPERMUNE-RE and the monitoring of specific antibody levels post transfusion in recipient foals.

In 2004, at a GLP licensed site, Veterinary Immunogenics commissioned an EU compliant Safety Study in which foals received plasma at 1-2 days of age and then approximately three weeks later. Daily monitoring was performed following both transfusions and resultant data re-affirmed the safety of the product.

Field studies during the 2003, 2004 and 2005 foaling seasons and subsequent laboratory analysis continued to support the observations documented by customers in the company's pharmaco-vigilance questionnaires of the efficacy of HYPERMUNE-RE. Furthermore, an efficacy study conducted in 2006 provided the largest sample population analysed to date (n=90). Results confirmed that administration of HYPERMUNE-RE significantly increased specific antibodies in recipient foals and markedly reduced the incidence of disease, requirement for antibiotic treatment and mortality rate, compared to foal groups that received normal plasma or no prophylactic treatment.

All of this work and investment has resulted in the UK regulatory authority (Veterinary Medicines Directorate) granting a UK National Marketing Authorisation for HYPERMUNE-RE in April 2007. This endorses the product as being of consistent high quality, safe and efficacious.

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Plasma Usage

The lower specification limit for R.equi antibodies in HYPERMUNE-RE has been validated at greater than or equal to 40% of Veterinary Immunogenics Standard. It is very important, however, to appreciate that high quality specific antibody plasma can only achieve the best prophylactic results when the timing of its administration is optimised. Knowledge of the particular seasonal pattern of foal exposure to R.equi in a specific geographic setting is required. When a normal healthy foal is administered plasma too early, it may experience a decline in antibody or other unknown protective plasma factors and may not therefore have protection at the time of environmental challenge. Failure of Passive Transfer or Partial Failure of Passive Transfer foals are likely to be even more vulnerable. While routine testing of foals at 24 hours of age for satisfactory IgG levels may be helpful in devising strategies for individual foals, in general it is considered not particularly advantageous, as it has been reported that there is no correlation between total serum IgG levels and the amount of R.equi specific antibody, and that colostrum derived specific R.equi antibody is not as protective as when R.equi antibody is administered via plasma (2). Each stud farm may well devise different strategies even in a similar geographic location, but preventive protocols for plasma must be based on the following:

- Plasma is administered prior to exposure to infection.
- High specific antibody levels are sustained throughout the high risk period.

In order to comply with these, equine veterinarians have devised their own schemes for preventing this disease. For example, in the most challenging situations in the USA, the administration of one litre intravenously at birth and a second litre at 30 - 45 days is reported to be 100% successful. On the other hand, a prophylactic programme recommended in another part of the world is to vaccinate mares prior to foaling, but still administer one litre of plasma at 25 days of age and again at 45 days of age to the foals to try to ensure immunity from birth to at least 70 days. In California, R.equi plasma is used just as the high risk dust period commences in March (6). Such a strategy has also been used successfully in the Middle East in 2004.

Successful preventive protocols should be devised to suit unique local conditions.

Taking these factors into account and in the absence of local epidemiological knowledge, it is essential to emphasise the importance of timing administration in relation to the period of challenge. A recent study has shown how the weather patterns influenced the occurrence of R.equi disease in foals on an endemic farm in 2006. The majority of foals were born in April-May, but the highest incidence of disease occurred in September, which coincided with an unexpected very warm and dry period where pathogenesis of the bacterium was probably facilitated via inhalation of contaminated dust particles from well worn pastures. This demonstrates that a natural decline in passively acquired specific antibody from either early season plasma or satisfactory colostrum transfer, coupled with an immature adaptive immune system in 4 month old foals may lead to a late season episode of clinical disease in high challenge situations.

Therefore, effective preventive protocols should be devised to suit unique local conditions by considering:

Predicted foaling pattern.
Predicted R. equi challenge period.
Abnormal weather influencing risk during the foaling season.
HYPERMUNE-RE plasma should then be administered to provide and sustain the key protective antibodies in the susceptible foal during its most vulnerable period, bearing in mind that the half-life of transfused antibodies is around 30-35 days (7). Finally, it should also be pointed out that the success of prophylaxis using plasma is greatly enhanced if it is part of an overall management strategy for the control of Rhodococcus equi infection (4).

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