SAFETY OF A NEW ATTENUATED IBR LIVE VACCINE WITH DOUBLE GENETIC DELETION gE-tk-
DISSEMINATION, LATENCY/RE-EXCRETION AND ABORTIGENICITY: 3 TRIALS ASSAYING
VERY HIGH DOSES
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INTRODUCTION

Eradication programs in the EU regarding Infectious Bovine Rhinotracheitis (IBR) are based mainly on a differentiation of infected from vaccinated animals (DIVA) strategy by using marker vaccines. So far, all these IBR marker vaccines were based on Bovine HerpesVirus-1 strains lacking glycoprotein E (single deleted BoHV-1 gE- strains).

At HIPRA we have developed and registered in the EU a new attenuated IBR vaccine (Hiprabovis® IBR Marker Live) which contains a BoHV-1 strain with a double genetic deletion gE-tk-. This viral strain features, as well as the gE deletion, which confers attenuation on the parental strain and allows for the serological marking, an extra deletion affecting the gene of the enzyme thymidine kinase (tk), as this confers also attenuation on the parental strain (1), reduces the probabilities of latency, reactivation, re-excretion and re-isolation in the field (2) and makes highly improbable the recovery of virulence after an event of herpesvirus spontaneous recombinantion (3).

This new IBR vaccine has widely demonstrate its safety through different trials, according to the strict requirements of European Pharmacopeia: recommended dose, repeated dose, overdose, transmission to unvaccinated animals, reversion to virulence, safety in pregnant cows, dissemination.

We present here three studies focused on demonstrating the safety of the new vaccine Hiprabovis® IBR Marker Live due to the intrinsic characteristics of the double deleted strain (strain CEDDEL) that contains:

Trial 1: dissemination, shedding and latency
Trial 2: latency, reactivation and re-excretion
Trial 3: abortigenicity and passage through the placenta.

MATERIALS AND METHODS

Animals: all the animals included in these trials were cross-bred Friesians, in good health status and free of BoHV-1 antigen and antibodies.

Vaccine: Hiprabovis® IBR Marker Live (strain CEDDEL, gE-tk-), HIPRA.

Virus detection: an extensive array of technics was applied to detect BoHV 1 in the samples:
- Isolation and titration by cell culture
- A new developed and validated specific differential PCR:
  - Specific for BoHV-1
  - Differentiation of gE+/gE- strains
  - Differentiation of tk+/tk- strains
- Immunohistochemistry.

Method:

Trial 1. Dissemination, shedding and latency after a very high vaccine overdose
6 seronegative calves (3 male and 3 female) were vaccinated with a very high vaccine overdose (>10exp8.3 CCID 50/calf). This result was identical whether the tissues were respiratory (nasal mucosa, trachea, lung), reproductive (testis, seminal vesicle, prostate, ovary, uterine mucosa, vaginal mucosa) or nervous (trigeminal ganglia), both by virus isolation and by specific differential PCR.

No dissemination, no shedding or latency of the vaccine virus. A summary of the results is presented in Table I below.

Trial 2. Latency, reactivation and re-excretion after vaccination and treatment with dexamethasone

The vaccine virus was not shed (was not re-excreted) after the dexamethasone treatment. Nasal swabs were negative for presence of BoHV-1, both by virus isolation and by specific differential PCR. In contrast, the positive control calves did shed high amounts of the virulent BoHV-1 strain after the dexamethasone treatment. Furthermore, neither infectious virus nor genetic material of BoHV-1 was detected in tonsils and in trigeminal ganglia of the vaccinated animals, further indicating a lack of latency of the vaccine virus.

Trial 3. Abortigenicity and passage through the placenta
22 cows remain well until the end of pregnancy giving birth to 23 healthy calves (there was a case of twins). The 2 cases of abortion were thoroughly investigated. There were no evidences of IBR infection in these abortions: no virus was detected in placenta or foetus by a number of technics, including immunohistochemistry. In contrast, a bacterial infection was determined in one of the abortions. All calves born to term were in good health and were completely seronegative to IBR antibodies before suckling the colostrum.

CONCLUSIONS

The safety of a new double deleted (gE-tk-) attenuated live IBR vaccine (Hiprabovis® IBR Marker Live, HIPRA) was demonstrated in relation to the intrinsic characteristics of the double deleted strain CEDDEL:

- There was no dissemination or shedding of the virus after vaccination with a very high overdose
- No latency (trigeminal ganglia) was detected in any trial
- After dexamethasone treatment there were no evidences of reactivation or viral re-excretion
- The vaccine virus is not abortigentic: it did not cross the placenta

REFERENCES