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What do we know about Equine Rotavirus Immunization and What are the Further Steps?

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Mini Review

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ABSTRACT

Rotavirus is the main cause of diarrhea in foals and other mammals. Prevention of rotaviruses in horses currently depends on inactivated vaccines parentally administrated to the dams in late gestation to enhance specific antibody levels in colostrum, since orally delivered live vaccines are often inactivated by maternal immunoglobulins. Despite inactivated vaccines have been commercially available since mid-1990s, rotaviruses are still the major cause of diarrhea in foals, which suggests that new vaccine alternatives should be considered. An ideal rotavirus vaccine would provide heterotypic immunity and protection against a wide variety of rotavirus serotypes. Although little progress has been observed in the development of equine rotavirus vaccines in recent years, research in the area have been carried out in other species. The development of subunit and cloned vaccines produced by viral or bacterial vectors has been proposed as a safe and promising alternative and may be a valuable alternative for foals immunization.

Keywords: Foals; Diarrhea; Viral infection; Vaccination; Virus

INTRODUCTION

Rotavirus is the main enteropathogen associated with diarrhea in foals, as in humans and other species [1-3]. Live attenuated oral vaccines have been widely used for children and have proven to be effective in the prevention of severe rotavirus diarrhea, although concerns continue about rare but severe cases of intussusception [4]. Since in neonatal foals orally delivered live vaccines are often inactivated by maternal immunoglobulins, prevention of equine rotaviral diarrhea is currently dependent on inactivated vaccines parentally administrated to the dams to enhance specific antibody levels in colostrum [5]. Despite inactivated vaccines have been commercially available since mid-1990s, rotaviruses are still the major cause of diarrhea in foals which suggests that new vaccine alternatives should be considered. This review briefly describes what is known about equine rotavirus vaccines and the future directions for the development of new vaccines.

LITERATURE REVIEW

Rotavirus structure and classification

Rotaviruses have an icosahedral structure, are non-enveloped RNA virus, and belong to the family Reoviridae, subfamily Sedoreovirinae, genus Rotavirus [6]. The virus genome consists of 11 segments that encode six structural proteins (VP1-VP4, VP6 and VP7) and six non-structural proteins (NSP1-NPS6). Each segment encodes one protein, with exception of the eleventh gene segment which encodes both NSP5 and NSP6 [7]. These viruses are classified into groups A-J, according to the intermediate capsid protein VP6 [8]. Only group A rotavirus had been detected in horses until 2021, when a group B rotavirus from ruminant origin was associated with a diarrhea outbreak in Central Kentucky. Despite this important episode of cross-transmission between species, the most relevant rotaviruses for horses are still from group A. It is worth noting that all group A rotaviruses share the same intermediate capsid, composed by VP6 protein [8,9]. The outer capsid of the virus is composed by the VP7 protein, which is considered the major neutralizing antigen and classifies group A rotaviruses into 27 G (glycoprotein) types. The viral spike is composed by the VP4 protein, which is a minor neutralizing antigen and classifies rotavirus in 35 different P (protease-sensitive) types [5,10]. Six G types (G3, G5, G8, G10, G13, G14) and six P types (P[1], P[3], P[7], P[11], P[12], P[18]) of group A rotaviruses have been detected in foals (bailey et al., 2013). Of these, G3P[12] and G14P[12] are the main genotypes affecting horses in many countries, while the other rotaviruses isolated in foals are considered rare cases of cross-transmission between species [5,11]. In addition, it is suggested that rotaviruses are generally host-specific and interspecies reassortments are uncommon [5].

Among rotavirus non-structural proteins, NSP4 stands out because its sequence is highly conserved among rotavirus genotypes [12]. This protein has been identified as a viral enterotoxin, which is secreted early after viral infection and

also have an important role in the viral particle maturation into the enterocyte [13,14]. It is suggested that vaccines including this protein may provide broad protection by neutralizing the enterotoxin of different rotaviruses [15].

What we know about equine rotavirus vaccines

There are three licensed vaccines for use in horses, developed in the United States, Japan and Argentina. The first two are monovalent and have strains of a G3 rotavirus, while the Argentinian vaccine is trivalent; however, it has only one rotavirus isolated from horses, which is also a G3 strain [5]. The three vaccines demonstrated an increase on specific antibody concentrations in vaccinated mares and their foals [16-18]. A field trial showed that 30% of foals born to mares vaccinated with the Argentinian vaccine had rotaviral infection, although duration of clinical signs was short and shedding not was detected [17]. In Japan, a study demonstrated that all foals born to mares vaccinated with the Japanese vaccine had neutralization antibody titers of 1:320 to 1:10,240 three days after foaling. In one of the evaluated farms, 16 of the 40 foals from vaccinated group developed diarrhea caused by a G14 rotavirus [18]. However, a more recent study performed in Japan showed that vaccinated mares produce virus-neutralizing antibodies against both G3BP[12] and G14P[12] strains, although only five mares were evaluated [19]. A field study of the immunogenicity and efficacy of the American vaccine showed that specific antibodies were significantly increased in vaccinated mares and their foals, although incidence of rotaviral diarrhea was not significantly different when compared to the control group [16]. More recently, a high rate of equine rotavirus infection (>80%) was detected in a horse population, although more than 50% of the dams had been vaccinated with the American vaccine as recommended by the manufacturer. Besides, G14 strains showed to be predominant among the equine population with significant antigenic differences in the outer capsid when compared to the American equine rotavirus vaccine strain [20]. As mentioned before, rotaviruses are still the major cause of diarrhea in foals despite the use of inactivated vaccines, and G14 strains seem to be more prevalent in horse populations nowadays [5].

Future directions for the development of new parenteral vaccines for equine rotavirus

An ideal rotavirus vaccine would provide heterotypic immunity and protection against a wide variety of rotavirus serotypes [5]. Although little progress has been observed in recent years regarding vaccines against equine rotavirus, research in the area have been carried out to improve commercial vaccines available for humans. The development of recombinant vaccines produced by viral or bacterial vectors has been proposed as a safe and promising alternative, including subunit and cloning vaccines [21,22]. The VP6 is the most abundant rotaviral protein and is mostly conserved among group A rotaviruses [5]. It has been demonstrated that multiple regions of VP6 expressed in *Escherichia coli* can stimulate protection and reduce viral shedding [23]. The co-expression of NSP4 and VP7 in adenovirus vector has also been shown to induce both humoral and cell-mediated immune response in mice [15]. Other approaches have been proposed including the use of rotavirus particle without the outer capsid proteins VP4 and VP7 and in some platforms combined with norovirus viral-like particles [24]. Also, a recombinant subunit parenteral rotavirus vaccine developed as a truncated recombinant VP8 protein of human rotavirus genotypes P[8], P[4] or P[6] expressed in *Escherichia coli* have demonstrated to elicit serum neutralizing immune response in animals. The immunogenicity was enhanced when the construction was fused to P2 epitope of tetanus toxoid, which elicits a strong T-cell helper function [25-27]. The level of diarrhea was noticeably lower in the foals in the immunized group than it was in the controls. Although the G14 serotype, which is distinct from the G3 vaccination strain, infected the vaccinated group foals on farm T, the clinical indications in this group were quite moderate. This implies that the G3 rotavirus vaccine can lessen the symptoms of diarrhea brought on by G14 serotype rotavirus infection. The latex

agglutination test demonstrated that foals in the control group had rotavirus infection. As a result, we were unaware of the rotavirus serotype that affected these foals. The etiology of G3 and G14 rotavirus infections in foals, however, is widely thought to be identical. Since G3 and G14 serotype rotavirus share the P[12] genotype, which codes for yet another neutralizing viral surface protein, we felt it was permissible to utilize the control-group foals as controls for the vaccinated-group foals. As a result, it is understood that these rotaviruses partially interact with one another. The isolated T-1 virus (G14 serotype) in our investigation also interacted with the vaccination strain, HO-5 (G3 serotype). Cross-reaction of the isolated virus with the vaccine strain may have contributed to the relatively mild diarrhea experienced by the foals on farm T who had received vaccinations. On the other hand, rotavirus infection caused diarrhea in 16 (or 40%) of the 40 foals in the vaccination group. The G14 serotype rotavirus, which was distinct from the strain used in the vaccine, may have been a significant factor in determining which foals experienced diarrhea.

CONCLUSION

Immunization of foals against equine rotavirus remains a challenge. Despite three commercial inactivated vaccines have been available and demonstrated to be able to produce specific antibodies, rotaviruses are still the major cause of diarrhea in foals. Different approaches for parenteral vaccination against rotavirus have been proposed in other species, including subunit and cloning vaccines, and these can be valuable for the development of new alternatives for foals' immunization.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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