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Rotarix® and RotaTeq® administration to preterm infants in the neonatal intensive care unit: Review of available evidence

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ABSTRACT

Rotavirus (RV) is the leading cause of severe acute gastroenteritis (GE) in infants worldwide. Several vaccines against RV were developed to reduce disease burden, hospitalization rates and health utilization costs. RV GE is a serious disease in preterm (PT) infants, and the administration of RV vaccine to these at-risk subjects at the proper time could have great clinical relevance. However, most data on the efficacy and safety of RV vaccinations were collected in healthy full-term infants, and few studies investigated PT infants. The lack of studies in PT infants may explain why neonatologists in several neonatal intensive care units (NICUs) do not follow the official recommendations, which indicate that RV vaccine may be administered in hospitals. Increasing neonatologists' knowledge on the efficacy and safety of RV vaccines and defining PT candidates for vaccination and the necessary precautions are extremely important to avoid potential vaccine virus transmission and improve RV vaccination coverage in PT infants. Further studies should analyse the impact of vaccination of PT infants of different gestational ages and various clinical histories in stable conditions in the NICU with a careful monitoring of adverse events to the vaccine and RV GE occurrence. Only data that confirm the efficacy and safety of RV vaccines in large numbers of PT infants with different characteristics will convince neonatologists to use RV vaccines in PT infants hospitalized in NICUs.

1. Introduction

Rotavirus (RV) is the leading cause of severe acute gastroenteritis (GE) in infants worldwide in the absence of prevention [1]. Several vaccines against RV were developed to reduce disease burden, hospitalization rates and health utilization costs [2]. Two oral preparations are licensed in industrialized countries: a live, attenuated, monovalent human RV vaccine (Rotarix®, RV1) [3] and a live, attenuated, pentavalent human-bovine reassortant RV vaccine (RotaTeq®, RV5) [4]. Other vaccines are licensed in India [5] and in China [6] but they are not registered in Europe and in America and are not discussed in this paper. RV1 must be administered as a two-dose schedule to ensure the highest protection, but three doses of RV5 are recommended. RV1 and RV5 are immunogenic and highly effective, as evidenced by the dramatic reduction in the incidence of RV AGE in children in all countries in which RV vaccinations were implemented [7]. Randomized, controlled prelicensure trials demonstrated that RV1 and RV5 were not associated with the development of serious adverse events, and solicited and unsolicited adverse events due to the vaccines were uncommon and mild [3,4]. Therefore, these vaccines were considered well tolerated and safe. However, post-marketing surveillance identified that both RV vaccines were associated with a slight but significant increase in the risk of developing intestinal intussusception. Initially, the risk was estimated to be 1–2 additional intussusceptions per 100,000 vaccinated infants, irrespective of which vaccine was used [8–17]. The extent of this risk was clearly dose and age-related because the incidence of intussusception was found higher after the first dose and tended to rise with the increasing age of the vaccinated infants, becoming marginal in subjects younger than 15 weeks [18]. Recently, a meta-analysis of the observational studies designed as self-controlled case series reported that the relative risk was 5.71 (95% confidence interval [CI], 4.50–7.251–7 days after the first dose) vs 1.69 (95% CI, 1.33–2.14 after the second) and 1.14 (95% CI, 0.75–1.74) after the third [19]. The occurrence of natural idiopathic intussusception increases with age, and it is marginal before the third month of life [18]. It has been calculated

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that without the RV vaccination, one child out of 5208 will have an intussusception during the first 3 months of life, whereas with the RV vaccination this will occur in one child out of 4785 [19]. This means that the risk-benefit equation between the efficacy of RV vaccines and adverse events incidence strongly favours the benefits [20], and RV1 and RV5 remain strongly recommended with some restrictions. Precise restrictions in administration time were provided and periodically modified according to the availability of new information on time limits beyond which the risk of intussusception tends to increase. Current USA guidelines suggest that the first dose of both vaccines must be given after the 6th week, but no later than the beginning of the 15th week, of postnatal age [21]. Further doses must be administered at intervals of 4–10 weeks. However, vaccination with RV1 must be completed no later than 24 weeks of age, and RV5 vaccinations must be completed before the end of the 8th month [21]. Similar schedules are recommended in several other countries [22].

Preterm (PT) infants frequently require hospitalization beyond the beginning of the 15th week of life, which suggests that they should receive RV vaccines during hospitalization according to the official immunization schedule. Stumpf et al. demonstrated that this problem includes approximately 20% of all of the PT infants admitted to neonatal intensive care units (NICUs), with the highest incidence in extremely low birth weight infants [23]. However, the systematic administration of RV vaccines during hospitalization in NICUs is controversial. Neonatologists do not systematically administer RV vaccines even when health authorities recommend administration. The present paper discusses the pros and cons of RV vaccination of hospitalized PT infants in the light of the available data on the need for RV vaccine use in PT infants and the immunogenicity, efficacy and safety of RV1 and RV5 in these patients.

2. Clinical relevance of rotavirus (RV) acute gastroenteritis in preterm (PT) infants

Most children are infected by RV by the age of 5 years, and most of these children develop a clinically evident acute GE, with the most severe cases occurring in patients who are 4–23 months old [24–26]. However, PT infants and infants with low birth weight (a likely proxy for prematurity) are at higher risk of severe disease even several months after birth compared to full-term (FT) infants and infants with normal birth weight. Severe dehydration, bloody stools, abdominal distension and necrotizing enterocolitis are more common in PT infants than FT infants [25,26]. RV infection outbreaks were described in hospitalized children, most prevalently in the NICU setting [27]. The increased clinical relevance of RV infection in PT infants was hypothesized in 1995 when a study of the causes of death of USA children found that a diagnosis of diarrhoea was frequently associated with prematurity [28]. The increased risk of severe RV GE in PT infants was definitively demonstrated several years later when one study demonstrated that hospitalization rates for RV diarrhoea in the first months of life were closely related to birth weight and tended to become greater with larger reductions in body weight [29]. Dennehy et al. recently reported the long-term effect of prematurity on RV diarrhoea occurrence and found that birth weight <2500 g was associated with approximately three times higher risk of hospitalization for RV AGE even beyond the first few months of life than infants with birth weights ≥2500 g (odds ratio [OR], 2.8; 95% confidence interval [CI], 1.6–5.0) [30].

Several factors may explain the increased severity of RV AGE in PT infants. First, PT infants possess an immature immune system and exhibit poor immune system function [31]. Medical interventions further impact immune development and function. Antenatal corticosteroid treatment may be immunosuppressive, and caesarean section affects an infant's gut and nasopharyngeal microbial colonization, which also alters immune function [31]. These factors favour infections. The poor transfer of maternal antibodies prior to birth also increases RV risk. Foetal IgG antibody levels are only 50% of maternal levels at 28–32 weeks of gestation. These levels continue to increase during the third trimester and reach maternal concentrations only in FT neonates [32]. The concentration of transferred anti-RV IgG antibodies is inversely correlated with the risk of RV infection, and severe prematurity is associated with the highest risk [33]. Finally, the reduced opportunity for breastfeeding and the protective role played by breast milk impact RV severity. The incidence and duration of breastfeeding in PT infants is lower than FT ones. This reduced breastfeeding is likely related to challenges for PT infants and parents, including establishing and maintaining a milk supply and transitioning from gavage feeding to breastfeeding [34]. Colostrum and early breast milk contain RV-specific antibodies and non-specific bioactive components (e.g., lactoferrin, lactadherin, mucin, and butyrophilin), which limit RV replication and reduce the risk of severe RV AGE [35,36]. Several studies demonstrated that breastfeeding is a protective factor against the development of severe RV GE [37–39].

3. Impact of rotavirus vaccines on preterm infants

Both RV vaccines were studied in PT infants, but a relatively small number of subjects were investigated. Available data suggest that RV1 and RV5 induce a protective immune response in PT subjects that is not substantially different from FT infants, without any increase in the incidence of adverse events.

Omenaca et al. evaluated the immunogenicity and safety of RV1 in a randomized, placebo-controlled study of 1009 PT infants of gestational ages between 27 and 36 weeks [40]. Anti-RV IgA seroconversion at 30–86 days post-dose 2 was evidenced in 85.7% of subjects, which is similar to FT infants in previous studies [41,42]. Seroconversion rates and mean anti-RV IgA antibody concentrations were lower in children with a gestational age ≤30 weeks compared to higher gestational age infants (seroconversion rate: 75.9% vs. 88.1%; IgA concentration: 236.5 U/mL vs. 359.1 U/mL). However, the differences were not statistically significant, and all of the studied immune parameters in PT infants were within the range of the immune responses observed in FT infants [40,43], which suggests that RV1 can protectPT infants regardless of gestational age. The incidence of adverse events was slightly higher after the first dose, but globally low. Serious adverse events (including fever, diarrhoea, vomiting and irritability) were recorded in approximately 5% of immunized PT infants and the placebo group, which is not substantially different from the values previously found in FT infants [43].

Goveia et al. first evaluated the safety and efficacy of RV5 in PT infants from data collected in a large-scale study that was specifically planned to evaluate RV5 safety and efficacy in the paediatric population [44,45]. A total of 2070 PT infants born at ≤36 weeks of gestational age were evaluated. Serious adverse events were recorded in approximately 5% of the cases, with no difference between immunized and placebo PT infants and with an incidence that was quite similar to FT infants [44,45]. RV5 was very effective because the rates of hospitalization and emergency department visits due to RV GE in the two years following the third dose of the vaccine was reduced by 100% in fully immunized PT infants. Roué et al. confirmed these findings in a more recent study [46]. These authors evaluated the impact of a vaccination programme using RV5 on the hospitalization rate for RV GE in a population of 217 children <3 years old who were born before 37 weeks of gestation. Data collected before and after the start of the vaccina-

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