Divergence of VP7 genes of G1 rotaviruses isolated from infants vaccinated with reassortant rhesus rotaviruses

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Summary. A large placebo-controlled efficacy trial of the rhesus tetravalent (RRV-TV) and serotype G1 monovalent (RRV-S1) rotavirus vaccines was conducted in 1991–1992 at 24 sites across the United States. Protection was 49% and 54% against all diarrhea but 80% and 69% against very severe gastroenteritis for the two vaccines, respectively. Post-vaccination neutralizing antibody titers to the G1 Wa strain, whose VP7 protein is nearly identical to that of the D strain of rotavirus contained in both vaccines, did not correlate with protection against subsequent illness with G1 strains. This result raised the possibility that in infants who developed post-vaccination neutralizing antibody to Wa, breakthrough (i.e., vaccine failure—the occurrence of rotavirus diarrhea after immunization) may have been due to infection by G1 strains that were sufficiently antigenically distinct from the vaccine strain to evade the neutralizing antibodies elicited by vaccination. To test this hypothesis, we initially compared post-vaccination neutralizing antibody titers of vaccinees against Wa and G1 breakthrough strains using sera from subjects who experienced breakthrough. Post-immunization neutralizing antibody titers to Wa elicited by vaccination were significantly (P < 0.001) greater than to the breakthrough strains subsequently obtained from these subjects. This difference did not, however, correlate with lack of protection since similar differences in titer to Wa and breakthrough strains were found using post-vaccination sera from vaccinees who either experienced asymptomatic rotavirus infections or no infections. To determine
the genetic basis for these differences, we compared the VP7 gene sequences of Wa with vaccine strain D, 12 G1 breakthrough strains, and 3 G1 control strains isolated during the same trial from placebo recipients. All breakthrough strains were distinct from Wa and D in antigenically important regions throughout the VP7 protein, but these differences were conserved between breakthrough and placebo strains. Furthermore, a comparative analysis of the deduced amino sequences from VP7 genes of G1 rotaviruses from 12 countries indicated that four distinct lineages have evolved. All breakthrough and control strains from the U.S. vaccine trial were in a lineage different from strain D, the serotype G1 vaccine strain. Although the overall results do not support our original hypothesis that immune selection of antigenically distinct escape mutants led to vaccine breakthrough in subjects with a neutralization response to Wa, it cannot be excluded that breakthrough could be partially due to antigenic differences in the VP7 proteins of currently circulating G1 strains.

Introduction

Group A rotaviruses are the most important etiologic agents of severe gastroenteritis in children, and as a result, the development of an effective vaccine against severe rotavirus diarrhea is a top public health priority [18]. Numerous rotavirus serotypes have been characterized on the basis of neutralizing antibodies to the outer capsid proteins VP7 (G-serotypes) and VP4 (P-serotypes), of which at least four G-serotypes and one P-serotype (composed of two subtypes, 1A and 1B) have been shown to be of major importance in human disease [10, 17, 32, 34, 37]. Antibodies to the VP7 and VP4 proteins protect against disease in animal models, suggesting that development of type-specific neutralizing antibodies may be important in protection against human illness [25]. Early observations that high levels of neutralizing antibodies to the infecting serotype correlated with protection against natural rotavirus disease in infants were consistent with this hypothesis and suggested that an effective vaccine would have to produce immunity to common human G types [2]. However, studies showing that type-specific protection is elicited by natural rotavirus infection are contradicted by other studies showing that symptomatic reinfection of individual infants with the same G-serotype is possible [26]. Whether reinfections occur because of antigenic variation of these strains due to short-lived immunity in infants who seroconverted to the primary infecting strain, or because titers of serum neutralizing antibody are not directly related to protection, is unknown.

The first rotavirus vaccine candidates were heterologous simian (RRV) and bovine (WC3 and RIT4237) rotavirus strains whose G-serotypes were different from 3 or all 4 of the most common rotaviruses isolated from children with diarrhea. These attenuated, live, oral ("Jennerian") vaccines failed to induce consistently heterotypic protection to common human rotavirus serotypes in some settings, reinforcing the hypothesis that serotype-specific immunity may be necessary [19]. In an effort to elicit neutralizing antibody to some of the most important human rotaviruses, reassortant strains with G1, G2, G3, and G4 VP7