MINIREVIEW

Challenges for Rotavirus Vaccines

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Last year the rotavirus (RV) field sustained a profound surprise and setback when the first licensed RV vaccine (Rotashield–Wyeth Ayerst) was withdrawn from the market because of its temporal association with very rare cases of intestinal intussusception which mostly occurred in the first week after administration of the first vaccine dose [reviewed in Nakagomi (2000)]. The impact of the RV vaccine on the total incidence of intussusception (attributable risk of Rotashield vaccine) has not yet been thoroughly evaluated but could be very small (Nakagomi, 2000). Nonetheless, given the reported strength of the temporal association, it seems unlikely that this vaccine will ever be reconsidered for widespread use in the United States. Hence, the need for a new vaccine or vaccines is great. Since the Rotashield vaccine also had minor side effects (low-grade fever in children, primarily after the first dose) (Vesikari et al., 1999) and induced incomplete protection (Bresee et al., 1999; Conner et al., 1996), the obstacles to the development of an ideal RV vaccine are not trivial (Table 1). In this brief review, we will address selected immunological problems associated with the development of a successful RV vaccine.

Studies in naturally infected children and in animals have shown that intestinal antibodies are pivotal in protection from RV reinfection (Conner et al., 1996; Coulson et al., 1992; Feng et al., 1994; Franco and Greenberg, 1999; Matson et al., 1993). As opposed to systemic memory antibody responses, antiviral intestinal IgA responses in people are generally of short duration (Coulson et al., 1992; Murphy, 1999) and this is one of the likely explanations for the high rate of reinfection and disease in young children and some adults (Conner et al., 1996; Velazquez et al., 1996). Because T-cell-independent B cell responses are short lived, it is tempting to speculate that, at least in the mouse model, the falling level of memory B cells in the gut is related to the recent finding that many of the IgA ASC of the intestines of mice are antigen-specific T-cell-independent B1 cells (Macpherson et al., 2000). RV-specific intestinal IgA has been shown to be produced in completely T-cell-deficient mice (Franco and Greenberg, 1999) and this response appears to be functional. However, the role of the short-lived T-cell-independent IgA response in immunocompetent mice (and people) remains unknown.

In studies performed in day-care centers and orphanages where antibodies to RV have been measured very shortly before a RV outbreak, intestinal and/or serum antibodies have correlated with protection against natural RV reinfection (Conner et al., 1996; Matson et al., 1993). RV-specific antibodies (stool IgA in particular) have also been correlated with protection in some (Coulson et al., 1992) but not in all other studies involving naturally infected as well as vaccinated children (Conner et al., 1996; Ward et al., 1997). In general, serum antibody levels have correlated better with protection following natural infection than following vaccination (Velazquez et al., 2000). Thus, at present we do not have a precise and reliable marker of protection induced by vaccination. This absence has been an impediment to the development of new RV vaccines since the only way of determining that a vaccine is effective is with extensive and expensive field trials (Conner et al., 1996; Ward et al., 1997). Fecal antibody levels have been measured in a few vaccine studies but have not correlated well with protection, perhaps because they have not been measured at the appropriate time or because of inherent technical problems with the measurement of fecal IgA (Conner et al., 1996). Since the technical difficulties in the measurement of fecal IgA are not absolute as is evidenced by the studies of naturally infected children (Coulson et al., 1992; Matson et al., 1993), future vac...
TABLE 1
Challenges of a Rotavirus Vaccine

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<tr>
<th>Features of an ideal vaccine</th>
<th>Associated problems</th>
<th>Possible solutions</th>
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<tr>
<td>Be available to children in developing countries that need it most (Bresee et al., 1999)</td>
<td>Likely high cost of current vaccines or vaccine candidates</td>
<td>Use of synthetic or other formulations that do not need refrigeration; produce vaccine locally in less developed countries</td>
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<td>Be tolerated and effective in very young children in developing as well as developed countries (Bresee et al., 1999; Newman et al., 1999)</td>
<td>(1) Minor (fever) side effects of the vaccine are not desirable</td>
<td>(1) Use of recombinant, DNA or inactivated RVs with or without enteric coating</td>
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<td>Be immunogenic in the presence of maternal (transplacental and milk) antibodies (Ward et al., 1997)</td>
<td>(2) The immune response of young children is not as efficient or well understood as that of adults</td>
<td>(2) Studies of the mucosal immune response in young children need to be performed</td>
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<td>Induce an intestinal immune response (Franco and Greenberg, 1999; Murphy, 1999)</td>
<td>Take of oral vaccines is diminished by the presence of maternal antibodies</td>
<td>Sequential oral and parenteral administration of the vaccine; vaccine strain not neutralized by maternal antibody</td>
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<td>A clear correlate of protection following vaccination has not been identified for any RV vaccine tested to date (Ward et al., 1997)</td>
<td>Mucosal IgA and probably intestinal T cell responses are short lived and relatively difficult to measure accurately</td>
<td>Administration of several doses of the vaccine; studies of mucosal memory T and B cells and fecal antibodies in children</td>
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<td>Induce immunity to the most prevalent viral serotypes (Bresee et al., 1999)</td>
<td>The only way of currently evaluating a new RV vaccine is with expensive field trials</td>
<td>Studies of intestinal memory T and B cells and intestinal RV-specific antibodies as correlates of protection</td>
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<td>Provide sustained levels in the gut of effector mechanisms (IgA/CTLs) to efficiently counter the short incubation period of RV (Conner et al., 1996)</td>
<td>Although not fully characterized, immunity to RV is to some degree serotype specific and emergence of new viral serotypes can occur</td>
<td>Studies of the importance of viral serotype in protection and of the emergence of new viral serotypes</td>
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Vaccine studies should include more and better validated measurements of RV-specific fecal IgA (Conner et al., 1996).

RV-specific serum IgA has not provided a consistent correlate of protection induced by vaccination (Ward et al., 1997). In mice, heterologous (nonmurine) RVs, at certain doses, can induce a systemic immune response without inducing a substantial mucosal response (Feng et al., 1994). In humans, up to 95% of the serum anti-RV IgA is monomeric and thus likely of systemic origin. This information provides a possible explanation for the existence of children who developed RV-specific serum IgA after vaccination with the Rhesus vaccine but were not protected. Presumably, in these cases, serum IgA was of systemic origin and not locally effective. Another possible explanation for why the presence of RV-specific serum IgA did not correlate with protection after vaccination is that the IgA antibodies induced by vaccination have a different specificity than those induced by natural infection. The lack of a clear correlation of serum-neutralizing antibodies with protection in the vaccine studies suggests that this could be the case (Ward et al., 1997). On the other hand, effectively vaccinated children with low levels of RV-specific serum IgA or neutralizing antibodies could have been protected by alternative immune mechanisms such as CTLs that have been shown to have modest protective effects in animal models (Franco and Greenberg, 1999). Our inability to identify effective surrogate markers of vaccine efficacy implies that other measurements of the immune response might be useful.

One alternative approach to detecting and quantitating local humoral immunity is to study blood-circulating antibody-secreting cells (ASC) that have been stimulated by antigens on mucosal surfaces and that are targeted back to those sites for local antibody secretion (Kantele, 1990). In animal models, ELISPOT assays of blood-circulating mononuclear cells have been clearly shown to provide good correlates of protection and to reflect the numbers and quality of the ASC in the intestine (Yuan et al., 1996). In humans, blood-circulating ASC have been useful to study the immunogenicity of RV vaccines (Isolauri et al., 1995), and their appearance has recently been shown to correlate with the presence of RV-specific IgA ASC in the small intestine of healthy children (Brown et al., 2000). It remains to be seen if the quantification of B-cell ELISPOTs will yield a better surrogate marker of protection induced by vaccination as has been suggested in studies with salmonella vaccines (Kantele, 1990). As opposed to the ELISPOT assay which generally measures only effector B cells, an alternative marker of protection induced by RV vaccines or natural infection might be obtained by the accurate measurement of the low levels of circulating mucosally committed memory RV-specific T and B cells induced by immunization. The methodologies
(based on ELISPOT or flow cytometry) to study individual memory B cells that express virus-specific surface immunoglobulin and individual antigen-specific T cells are now available (Kuklin et al., 2000, 2001).

Finally, although it is widely acknowledged that differences in the immune response between very young children and adults exist, these differences have not been well defined in general or for RV immunity in particular. Most studies in this area have been based on observations in mice that cannot be directly extrapolated to humans because they have a very different ontological development. Our lack of knowledge of how the immune response of young children is generated or maintained to a mucosal pathogen like RV is probably an important impediment in the development of optimal vaccine strategies.

REFERENCES


