Rotavirus Serum IgA Immune Response in Children Receiving Rotarix Coadministered With bOPV or IPV

Sasirekha Ramani, PhD, Nora Mamani, Med Tech,† Rodolfo Villena, MD,‡ Ananda S. Bandyopadhyay, MBBS,§ Chris Gast, PhD,¶ Alicia Sato, MS,¶ Daniel Laucirica, BS,† Ralf Clemens, MD,‖ Mary K. Estes, MD,* and Miguel L. O'Ryan, MD†*

Background: Vaccine schedules including bivalent oral and inactivated poliovirus vaccines will replace trivalent oral poliovirus vaccines in 2016.

Methods: We evaluated rotavirus immunoglobulin A seroresponses when the second dose of Rotarix at 16 weeks was given concomitantly with inactivated or bivalent oral poliovirus vaccines.

Results: Rotavirus immunoglobulin A seroresponse rate at week 28 was 15% lower in recipients of bivalent oral poliovirus vaccines compared with inactivated poliovirus vaccines.

Conclusion: Bivalent oral poliovirus vaccine decreases rotavirus IgA seroresponse rates when coadministered at 16 weeks of age.

Key Words: rotavirus, poliovirus, vaccine, coadministration, seroresponse, antirotavirus immunoglobulin A, interference

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The World Health Organization currently recommends a combination or injectable inactivated poliovirus vaccines (IPVs) and oral poliovirus vaccines (OPVs) for routine infant immunization in most countries as part of the endgame strategy until interruption of all wild-type polioviruses has been certified globally.[1] A key element of this strategy is the sequential withdrawal of live attenuated OPV vaccine, beginning with type 2 poliovirus. The rationale behind this withdrawal is that wild-type 2 poliovirus circulation has not been detected since 1999 and has been certified to be eradicated. In addition, approximately one third of all vaccine-associated paralytic polio cases are caused by type 2 vaccine viruses. Thus, the Global Polio Eradication Initiative has recommended replacement of trivalent oral poliovirus vaccine (tOPV) with bivalent oral poliovirus vaccine (bOPV, types 1 and 3) by April 2016 accompanied by cessation of any elective use of type 2 containing OPVs. World Health Organization also recommends that all countries add at least 1 dose of IPV to their schedule, in preparation for this global shift to bOPV to ensure protection against type 2 polioviruses without any added risk of introducing vaccine-related type 2 disease. For the Americas, the Pan American Health Organization has adopted this general recommendation, proposing for the region the shift to an IPV/IPV/bOPV schedule for the primary series as the first option, and IPV/bOPV/bOPV as the second. (Guía Práctica: Introducción de la vacuna inactivada contra la poliomielitis (IPV). Washington, DC: OPS, 2014.)

For rotavirus, World Health Organization currently recommends vaccination for all infants, worldwide.[2] It has been observed, however, that rotavirus vaccines (RVs) have a lower immunogenicity and efficacy/effectiveness in developing countries, where the burden of rotavirus disease is the greatest.[3] Furthermore, a few studies suggest that OPV coadministered with RVs can interfere with the immunogenicity of the latter.[4–10] These studies have been diverse in the nature of the vaccines used, the time points of serologic evaluations and the serologic markers used. Nevertheless, most studies conclude that coadministration of an OPV with an RV will decrease antirotavirus immunoglobulin A (IgA) seroconversion rates and titers, with a few studies suggesting that this effect may be more relevant at the time of the first dose.[5,7] Although one study indicates that coadministration of the monovalent RV and tOPV may not have an effect on vaccine efficacy,[11,12] the fact that this interference may account, in part, for the differences in efficacy/effectiveness observed in lower socioeconomic regions, where tOPV is more commonly used, cannot be ruled out.

As many countries will move imminently to sequential or concomitant IPV-bOPV schedules, it is important to know how the administration of RVs and its immunogenicity are affected by such new regimens. Data on rotavirus immunogenicity when used in IPV-bOPV schedules do not exist. Chile currently uses a 3-dose tOPV schedule in its primary polio immunization series, has achieved high vaccine coverage (90%)[13] and many other countries in the region will follow the recommendations of Pan American Health Organization and use 1 or 2 doses of IPV followed by bOPV.

We previously carried out a study to assess the immunogenicity of 2 different IPV-bOPV schedules compared with an all-IPV schedule in Chilean infants observing that regimens incorporating 1 or 2 doses of IPV provided serotype 2 seroresponses of 77.4% and 96%, respectively, providing policy makers with reasonable assurance for schedules containing 1 or 2 IPV doses.[14] Importantly, seroresponse rates to rotavirus vaccination was included as an exploratory objective of this trial, aiming to determine if antirotavirus IgA seroconversion rates differed after a full course of 2 doses of the monovalent RV (Rotarix), administered at 16 weeks of age with either bOPV or IPV in children receiving a first dose administered with IPV at 8 weeks of age. Interference of bOPV with oral RV at the time of the second dose could lead some policy makers to favor use of IPV over bOPV at 16 weeks.

METHODS

Study Design and Participants

This analysis was carried out as a part of a larger phase 4 study that assessed humoral and intestinal immune responses of

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From the *Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, Texas; †Faculty of Medicine, Microbiology and Mycology Program, Institute of Biomedical Sciences; ‡Faculty of Medicine, Department of Pediatrics, Exequiel González Cortes Hospital, Universidad de Chile, Santiago, Chile; §Bill & Melinda Gates Foundation, Seattle, WA; ¶Fred Hutchinson Cancer Research Center, Seattle, Washington; and ‖Global Research in Infectious Diseases, Rio de Janeiro, Brazil.

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Address for correspondence: Miguel L. O'Ryan, MD, Faculty of Medicine, Microbiology and Mycology Program, Institute of Biomedical Sciences, Universidad de Chile, Independencia 1027, Independencia, Santiago, Chile. E-mail: moryan@med.uchile.cl.

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various polio vaccine schedules; full details on the study can be found in O'Ryan et al.[14]

The study was multicentric, randomized and vaccinator-open but immunogenicity assessor-blind. Healthy infants who attended well child care visits at 6 community health-care centers in Santiago, Chile and who were due for their first dose of polio vaccine were eligible for the study. Further inclusion and exclusion criteria are available in the supplement to O'Ryan et al.[14] Informed consent and protocol were approved by local ethics committees of the Faculty of Medicine at the University of Chile, the Service de Salad Metropolitan Norte and the Service de Salad Metropolitan Sur (all located in Santiago, Chile).

Healthy, full-term infants at 8 weeks (±7 days) of age were randomized and allocated (1:1:1) to one of three treatment groups: (1) IPV at week 8, followed by bOPV at weeks 16 and 24 (IPV-bOPV-bOPV); (2) IPV at weeks 8 and 16, followed by bOPV at week 24 (IPV-IPV-bOPV); or (3) IPV at weeks 8, 16 and 24 (IPV-IPV-IPV). All three groups received oral RV (Rotarix) at weeks 8 and 16. Blood samples were analyzed for antirotavirus IgA antibodies at week 8 (before any vaccination) and at week 28 (4 weeks after completing the full course of the polio vaccinations).

Serum Antirotavirus IgA Detection

Serum samples were tested for antirotavirus IgA using an in-house antibody sandwich enzyme-linked immunosorbent assay based on previously described protocols.[15] Briefly, 96-well microtiter plates were coated overnight with hyperimmune serum from rabbits immunized with purified bovine rotavirus strain WC3. This was followed by addition of WC3 virus lysate or mock-infected MA104 cell lysate as antigens. Dilutions of a standard serum pool (assigned an arbitrary concentration of 5000 U), test samples and controls were added to the captured antigens. All test samples were run in a minimum of 2 dilutions (1:20 and 1:200) while a single dilution of a positive control sample was run on each plate as an internal reference. IgA was detected using biotinylated rabbit antihuman IgA, followed by peroxidase-conjugated avid in-biotin, and *O*-phenylenediamine, and dihydrochloride as substrate. The IgA titer of test samples was determined by interpolation from the linear portion of the standard curve obtained using the standard serum pool. Calculations were made using the 4-parameter logistic curve in GraphPad Prism 6.0. Samples with titers below the limit of detection (<32 U) were considered as negative for antirotavirus IgA. Week 8 seropositivity was defined as a positive titer at week 8. Week 28 seroconversion was defined as either a negative sample at week 8 and a positive titer at week 28, or positive titer at week 28 that is >4-fold over the positive titer at week 8.

Statistical Analysis

Rates of antirotavirus IgA seroconversion and median $\log_{10}$-antibody titer for group 1 (infants receiving bOPV together with the second dose of Rotarix at 16 weeks of age) were compared using the Fisher Exact Test with those from group 2 and 3 combined (infants receiving this second Rotarix dose together with IPV). Each of the 2 comparisons (null hypothesis of equality) was conducted with 2-sided alpha level of 0.05. These tests were supplemented with a 2-sided Wilcoxon rank-sum test of IgA antibody titers, as well as informal comparison of the reverse cumulative distribution curves of rotavirus IgA antibody titers.

RESULTS

Paired serum samples were available for 434 of a total of 570 infants enrolled in the original study. Demographic and social behavior characteristics were comparable between study treatment groups (see Text and Table, Supplemental Digital Content 1, http://links.lww.com/INF/C505, for details).

Four to eight percent of subjects were seropositive by 8 weeks of age in a baseline sample, with no differences between groups (Table 1). Antirotavirus IgA seroconversion rates at 28 weeks of age, 12 weeks after completing the RV scheme of 2 RV doses, were significantly lower in the group receiving concomitant bOPV administration at the time of the second rotavirus dose (group 1) compared with groups receiving IPV coadministration (groups 2 and 3; $P = 0.004$; Table 1, A). Seroconversion rates in groups 2 and 3 were similar (Table 1, B). Although overall antirotavirus IgA antibody titers achieved at 28 weeks were significantly

TABLE 1. Antirotavirus IgA Responses and Median Log_{10}-Antibody Titer Overall and Among Positive Responders at 8 and 28 Weeks for Group 1 Versus Groups 2 and 3 (A) and for Group 2 Versus Group 3 (B)

A

	Group 1		Groups 2, 3		
Endpoint	% (95% CI)	n/N	% (95% CI)	n/N	*P*
Week 8 seropositivity	6% (3.3%, 11.4%)	(9/145)	6% (3.7%, 9.2%)	(17/289)	1.000
Week 28 seroconversion	50% (42.3%, 58.4%)	(73/145)	65% (59.7%, 70.6%)	(189/289)	0.004
Week 28 median $\log_{10}$ IgA titer units (IQR) overall	1.8 (1.2)		2.1 (1.3)		0.007
Week 28 median $\log_{10}$ IgA titer units (IQR) among those seropositive at week 28	2.4 (0.7)		2.4 (0.6)		0.680

B

	Group 2		Group 3		
Endpoint	% (95% CI)	n/N	% (95% CI)	n/N	*P*
Week 8 seropositivity	4% (1.6%, 8.2%)	(5/138)	8% (4.6%, 13.4%)	(12/151)	0.139
Week 28 seroconversion	63% (54.7%, 70.6%)	(87/138)	68% (59.7%, 74.5%)	(102/151)	0.459
Week 28 median $\log_{10}$ IgA titer units (IQR) overall	2.0 (1.3)		2.2 (1.3)		0.156
Week 28 median $\log_{10}$ IgA titer units (IQR) in among those seropositive at week 28	2.3 (0.7)		2.4 (0.5)		0.797

Group 1 receiving Rotarix and bOPV concomitantly at week 16. Groups 2 and 3 receiving Rotarix and IPV concomitantly at week 16.
CI indicates confidence interval; IQR, interquartile range.

higher in groups 2 and 3 compared with group 1, this was a reflection of the seroconversion result, as median $\log_{10}$-antibody titers achieved among those seropositive at week 28 were similar between all groups (Table 1, A and B).

DISCUSSION

Infants receiving a full course of 2 doses of Rotarix at 8 and 16 weeks of age, of which the first was coadministered with IPV and the second with bOPV, had a 15% lower antirotavirus IgA seroconversion rate compared with infants receiving an all IPV regimen. Antirotavirus antibody concentrations in seroresponders after the 2 RV doses were not affected by the choice of the polio vaccine coadministered. This is important new data as it shows that not only the currently used tOPV but also the bOPV could interfere with the take of an oral RV. This information is important to guide decisions about coadministration of RV with the new polio vaccination options of IPV and bOPV to ensure not only an optimal polio schedule but also adequate protection of the majority of infants against rotavirus infection, the leading cause of childhood diarrhea morbidity and mortality.

Potential limitations of this study are that, despite using an antirotavirus IgA enzyme-linked immunosorbent assay protocol similar to other studies with Rotarix, the longer time gap from second dose of rotavirus vaccination to sample collection for IgA testing in addition to differences in the standard serum pool and choice of virus lysate for IgA testing may difficult comparison of results from this study to previous reports. However, a high degree of correlation in IgA levels was seen when a panel of samples were tested with lysates from different rotavirus strains.[16] Further, the seroconversion rates in this study were comparable to previous reports with Rotarix in South America.[17]

Individual country adoption of 2 or 1 IPV dose(s) followed by bOPV in future vaccine schedules as recommended by global policy makers will depend on several issues, and the fact that bOPV at 4 months decreases rotavirus immune response may influence such decisions in some countries.

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