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REFERENCES

1. Gershon A, Mervish N, LaRussa P, et al. Varicella-zoster virus infection in children with underlying HIV infection. *J Infect Dis.* 1997;176:1496-1500.
2. Son M, Shapiro E, LaRussa P, et al. Vaccination of children with perinatal HIV infection protects against varicella and zoster. Paper presented at: Pediatric Academic Societies Annual Meeting; May 3, 2008; Honolulu, HI.
3. Wood SM, Shah SS, Steenhoff AP, et al. Primary varicella and herpes zoster among HIV-infected children from 1989 to 2006. *Pediatrics.* 2008; 121:e150-e156.
4. Derryck A, LaRussa P, Steinberg S, et al. Varicella and zoster in children with human immunodeficiency virus infection. *Ped Inf Dis J.* 1998;17:931-933.
5. von Seidlein L, Gillette SG, Bryson Y, et al. Frequent recurrence and persistence of varicella-zoster virus infections in children infected with human immunodeficiency virus type 1. *J Pediatr.* 1996;128:52-57.
6. Levin MJ, Anderson JP, Seage GR III, et al; for the PACTG/IMPAACT 219C Team. Long-term and short-term effects of highly active antiretroviral therapy on the incidence of herpes zoster in HIV-infected children. *J Acquir Immune Defic Syndr.* 2009;50:182-191.
7. Levin M, Murray M, Rotbart H, et al. Immune response of elderly individuals to a live attenuated varicella vaccine. *J Infect Dis.* 1992;166:253-259.
8. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med.* 2005;352: 2271-2284.
9. Levin MJ, Oxman MN, Zhang JH, et al. Varicella-zoster virus-specific immune responses in elderly recipients of a herpes zoster vaccine. *J Infect Dis.* 2008;197:825-835.
10. Weinberg A, Wiznia AA, LaFleur BJ, et al. Varicella-zoster virus-specific cell-mediated immunity in HIV-infected children receiving highly active antiretroviral therapy. *J Infect Dis.* 2004;190:267-270.
11. Levin MJ, Gershon AA, Weinberg A, et al. Immunization of HIV-infected children with varicella vaccine. *J Pediatr.* 2001;139:305-310.
12. Levin MJ, Gershon AA, Weinberg A, et al. Administration of live varicella vaccine to HIV-infected children with current or past significant depression of CD4(+) T cells. *J Infect Dis.* 2006;194:247-255.
13. Bekker V, Westerlaken GH, Scherpbier H, et al. Varicella vaccination in HIV-1-infected children after immune reconstitution. *Aids.* 2006;20:2321-2329.
14. Michalik DE, Steinberg SP, LaRussa PS, et al. Primary vaccine failure after 1 dose of varicella vaccine in healthy children. *J Infect Dis.* 2008;197:944-949.
15. Williams V, Gershon A, Brunell P. Serologic response to varicella-zoster membrane antigens measured by indirect immunofluorescence. *J Infect Dis.* 1974;130:669-672.
16. Smith JG, Levin M, Vessey R, et al. Measurement of cell-mediated immunity with a varicella-zoster virus-specific interferon-gamma ELISPOT assay: responses in an elderly population receiving a booster immunization. *J Med Virol.* 2003;70(suppl 1):S38-S41.
17. Hayward AR, Zerbe GO, Levin MJ. Clinical application of responder cell frequency estimates with four years of follow up. *J Immunol Meth.* 1994;170: 27-36.
18. Levin MJ, Smith JG, Kaufhold RM, et al. Decline in varicella-zoster virus (VZV)-specific cell-mediated immunity with increasing age and boosting with a high-dose VZV vaccine. *J Infect Dis.* 2003;188:1336-1344.
19. Brady K, Levin MJ, Weinberg A, et al. Safety and Immune response to varicella vaccine in HIV-infected adults previously infected with varicella. In:

Program and Abstracts of the 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, WA. Abstract 608-W.

20. Brady K, Weinberg A, Lacy K, et al. Safety and immune response of varicella vaccine in HIV-infected adults with a history of immune compromise and prior infection with varicella. In: Program and Abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2004; San Francisco, CA. Abstract 773.

PHASE-I STUDY MEDI-534, OF A LIVE, ATTENUATED INTRANASAL VACCINE AGAINST RESPIRATORY SYNCYTIAL VIRUS AND PARAINFLUENZA-3 VIRUS IN SEROPOSITIVE CHILDREN

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**Abstract:** A live, attenuated respiratory syncytial virus and parainfluenza virus type 3 vaccine was evaluated in healthy respiratory syncytial virus/parainfluenza virus type 3 seropositive children aged 1 to 9 years. Three cohorts of 40 children were randomized 1:1 to receive 10<sup>6</sup>, 10<sup>5</sup>, or 10<sup>6</sup> median tissue culture infectious dose<sub>50</sub> MEDI-534 vaccine or placebo. The vaccine's safety profile was similar to placebo, no viral shedding was detected, and the vaccine was minimally immunogenic.

**Key Words:** RSV, PIV3, vaccine, children, safety profile

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Respiratory syncytial virus (RSV) and human parainfluenza virus type 3 (hPIV3) are respiratory pathogens, which cause annual bronchiolitis and pneumonia epidemics in young children worldwide. Based on the 2000 US Census data, the annual RSV and PIV3 medical burden in children younger than 24 months of age is estimated to be 2.7 and 2.47 million cases of medically attended acute respiratory illness, 1.36 and 0.82 million cases of lower respiratory tract infection, and 106,000 and 18,000 hospitalizations, respectively.<sup>1</sup>

Receipt of formalin-inactivated RSV vaccine was associated with severe disease; however, live, attenuated RSV and PIV3 vaccines as a class have not been associated with enhanced disease.<sup>2-5</sup> Moreover, live, attenuated RSV and PIV3 vaccines induce an immune response that includes serum and mucosal virus-neutralizing antibodies.<sup>6</sup>

MEDI-534 is a live, attenuated, intranasal vaccine against RSV and PIV3. It is a chimeric bovine/human (b/h) PIV3 construct that expresses the hPIV3 fusion (F), the hPIV3 hemagglutinin-neuraminidase, and the RSV F proteins from a bPIV3 viral genome.<sup>7,8</sup> MEDI-534 was immunogenic and provided protection

on challenge with wild-type virus in RSV and PIV3 seronegative hamsters and monkeys.<sup>8,9</sup> Additionally, in a phase-I study, MEDI-534 exhibited an acceptable safety profile in human adults.<sup>10</sup>

The primary objective of this study was to describe the safety profile and tolerability of a single intranasal dose of MEDI-534 when administered to healthy RSV/PIV3 seropositive children 1 to 9 years of age; the secondary objectives were to describe the immunogenicity and vaccine viral shedding of MEDI-534.

## PATIENTS AND METHODS

**Vaccine Preparation.** Vaccine virus was recovered from Vero cells using plasmid rescue procedure and was further expanded in Vero cells as previously described by Tang et al.<sup>10</sup> AccuSpray sprayers were filled with a 0.2 mL single intranasal dose of MEDI-534 containing  $10^4$ ,  $10^5$ , or  $10^6$  median tissue culture infectious dose (TCID<sub>50</sub>).

**Study Design.** This was a phase-I, randomized, double-blind, placebo-controlled, dose-escalation, multicenter (N = 6) study. The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board at each study site.

**Study Population.** One hundred twenty 1 to 9-year-old children were enrolled at 6 sites in Nebraska, Pennsylvania, West Virginia, New York, and Ohio (2 sites) from June 9, 2006 to May 15, 2007. The main inclusion criterion was healthy children who were seropositive for RSV and PIV3 (ELISA titer >12 U/mL [IBL-America, Minneapolis, MN used according to manufacturer's instruction] and hemagglutination inhibition titer >1:8, respectively) at screening 14 days before randomization. Children were excluded if they had inactivated or live attenuated vaccine within 14 or 30 days, respectively, before randomization, fever ( $\geq 100.7^\circ\text{F}$  tympanic or rectal, or  $\geq 100.1^\circ\text{F}$  oral), respiratory illness, or any drug therapy within 7 days before randomization. Additionally, children were excluded if they had known or suspected impairment of immunologic functions or were receiving immunosuppressive therapy. Three cohorts of 40 subjects were randomized at a 1:1 ratio to receive either a single 0.2 mL intranasal dose containing approximately  $10^4$ ,  $10^5$ , or  $10^6$  TCID<sub>50</sub> of MEDI-534 or 0.2 mL placebo. Block randomization was done by study site. Cohort progression was performed in a step-wise fashion and a blinded safety profile assessment occurred before each dose escalation. Subjects' parent/legal representative signed a written informed consent for their child's study participation before conducting seroscreening. Additionally, children 7 to 9 years of age provided written assent before study entry.

**Follow-Up.** The duration of study participation was from vaccination at day 0 through 180 days postvaccination.

**Safety Profile Outcomes.** Data for solicited events ([SEs], events specifically sought and assessed daily), adverse events (AEs), and concomitant medications were collected from the time of vaccination through day 28. Data for serious adverse events (SAEs) and significant new medical conditions were collected through day 180. Hematology (CBC with platelets and differential) and serum chemistries (AST, ALT, BUN, and creatinine) were evaluated at screening and on day 7.

**Vaccine Viral Shedding.** Nasal swabs and washes were obtained at days 3, 7, 14, and once between days 28 to 35 to assess vaccine virus replication using viral culture. Specimens were cultured on Vero cell monolayers and observed for viral-induced cytopathic effect and/or hemadsorption using guinea pig red blood cells. Samples from symptomatic subjects at the time of collection were cultured on RMK, Hep-2, MRC-5, and R-mix shell vials (Diagnostic Hybrids, Athens, OH). Positive cultures were confirmed by direct immunofluorescence.

**Immunogenicity.** Immune response was evaluated by measuring serum antibodies independently of the screening assays. For RSV microneutralization, serial 2-fold dilutions of serum were made and a standard GFP-RSV titer was added. After incubation for 1 hour at  $37^\circ\text{C}$ , the serum-virus mixtures were inoculated onto confluent washed Vero cells in 96-well plates and incubated for 48 hours at  $37^\circ\text{C}$ . The neutralizing titer was defined as the last well showing absence of fluorescence. The PIV3 hemagglutination inhibition assay was performed by incubating guinea pig erythrocytes with a 2-fold serial dilution of test serum. Titers were expressed as the mean reciprocal log 2 of the highest serum dilution that inhibited agglutination.<sup>10</sup> Serum samples were obtained immediately before vaccination on day 0 and once between days 28 to 35 post dosing.

## RESULTS

**Demographics.** Subjects' demographics were similar in the MEDI-534 and placebo groups. Mean age was  $5.9 \pm 2.4$  years (range: 1–9 years). The MEDI-534 and placebo groups had 53% and 33% boys, respectively. All 120 subjects had safety data available for analysis through days 28 and 180. Although 5 subjects exited on day 179 (site miscalculation), they were considered to have completed the study.

**Safety Profile.** Administration of a single intranasal dose of MEDI-534 at  $10^4$ ,  $10^5$ , or  $10^6$  TCID<sub>50</sub> had an acceptable safety profile in seropositive children. There were no medically attended-lower respiratory illnesses reported during the 28-day safety period, and no vaccine-related significant new medical conditions or SAEs occurred in the 180 days after vaccination.

**Serious Adverse Events.** Three vaccine-unrelated SAEs were reported following vaccination: traumatic arm fracture in the  $10^5$  TCID<sub>50</sub> MEDI-534 group, viral-culture negative pneumonia requiring 3 days of hospitalization in the  $10^6$  TCID<sub>50</sub> MEDI-534 group, and gastroenteritis requiring 2 days hospitalization in the  $10^4$  TCID<sub>50</sub> placebo group. All SAEs resolved without sequela.

**Solicited Events.** Most SEs in the MEDI-534 group were of mild/moderate severity, of short duration (lasting a median of 4 vs. 5 days in placebo), and resolved without treatment or with over-the-counter medication (Table 1). Three severe (grade 3) SEs were reported; all were fever  $\geq 101.9^\circ\text{F}$ . Two occurred in the  $10^5$  TCID<sub>50</sub> and  $10^6$  TCID<sub>50</sub> MEDI-534 recipients due to gastroenteritis (day 18) and acute otitis media (day 6), respectively, and one in the  $10^5$  TCID<sub>50</sub> placebo group due to enteroviral infection (day 22). Additionally, self-limited mild epistaxis occurred in one subject in the placebo group and 2 subjects in the  $10^6$  TCID<sub>50</sub> MEDI-534 group; one occurred on day 0 (associated with facial trauma) and the other on day 25.

**Adverse Events.** The incidence of unsolicited AEs occurred at similar rates in the MEDI-534 and the placebo groups (22/60 or 36.7% vs. 30/60 or 50%, respectively). The AEs in the MEDI-534 group had no apparent dose-response relationship, all were mild/moderate in severity, and resolved mostly without treatment. Two subjects in the  $10^6$  TCID<sub>50</sub> MEDI-534 group were diagnosed with acute otitis media (diagnosed on day 4 and 7; resolved by day 14 and 11, respectively). No vaccine virus or other respiratory virus was isolated from either subject. Both events were considered vaccine-related due to temporal association and resolved with oral antibiotic therapy. There were no clinically significant hematologic or blood chemistry abnormalities among MEDI-534 recipients. Other AEs reported in more than a single MEDI-534 recipient included abdominal pain 3.3% (vs. 3.3% placebo), diarrhea 3.3% (vs. 3.3% placebo), vomiting 5% (vs. 8.3% placebo), and increased temperature  $< 100.1^\circ\text{F}$  6.7% (vs. 5.0% placebo).

**TABLE 1.** Incidence of Solicited Events 0-28 Days Postvaccination

| SEs  | Cohort 1 (10 <sup>4</sup> TCID <sub>50</sub> ) |                 | Cohort 2 (10 <sup>5</sup> TCID <sub>50</sub> ) |                 | Cohort 3 (10 <sup>6</sup> TCID <sub>50</sub> ) |                 | Total           |                 |
|--|--|-----------------|--|-----------------|--|-----------------|-----------------|-----------------|
|  | MEDI-534                                       | Placebo         | MEDI-534                                       | Placebo         | MEDI-534                                       | Placebo         | MEDI-534        | Placebo         |
|  | N = 19<br>n (%)                                | N = 21<br>n (%) | N = 21<br>n (%)                                | N = 19<br>n (%) | N = 20<br>n (%)                                | N = 20<br>n (%) | N = 60<br>n (%) | N = 60<br>n (%) |
| Total number of SEs  | 18   | 38              | 59   | 71              | 41   | 27              | 118             | 136             |
| Number of subjects reporting ≥1 SE   | 7 (36.8%)                                      | 13 (61.9%)      | 16 (76.2%)                                     | 15 (78.9%)      | 14 (70.0%)                                     | 11 (55.0%)      | 37 (61.7%)      | 39 (65.0%)      |
| Fever  |  |                 |  |                 |  |                 |                 |                 |
| ≥100.1°F oral or ≥100.7°F tympanic/rectal                                    | 1 (5.3%)                                       | 4 (19.0%)       | 2 (9.5%)                                       | 1 (5.3%)        | 3 (15.0%)                                      | 1 (5.0%)        | 6 (10.0%)       | 6 (10.0%)       |
| ≥100.9°F oral or ≥101.5°F tympanic/rectal                                    | 1 (5.3%)                                       | 2 (9.5%)        | 2 (9.5%)                                       | 1 (5.3%)        | 1 (5.0%)                                       | 0 (0.0%)        | 4 (6.7%)        | 3 (5.0%)        |
| ≥101.9°F oral or ≥102.5°F tympanic/rectal                                    | 0 (0.0%)                                       | 0 (0.0%)        | 1 (4.8%)                                       | 1 (5.3%)        | 1 (5.0%)                                       | 0 (0.0%)        | 2 (3.3%)        | 1 (1.7%)        |
| >104.3°F oral or >104.9°F tympanic/rectal                                    | 0 (0.0%)                                       | 0 (0.0%)        | 0 (0.0%)                                       | 0 (0.0%)        | 0 (0.0%)                                       | 0 (0.0%)        | 0 (0.0%)        | 0 (0.0%)        |
| Sore throat <sup>†</sup>   | 1 (5.3%)                                       | 5 (23.8%)       | 8 (38.1%)                                      | 4 (21.1%)       | 6 (30.0%)                                      | 2 (10.0%)       | 15 (25.0%)      | 11 (18.3%)      |
| Wheeze   | 0 (0.0%)                                       | 0 (0.0%)        | 0 (0.0%)                                       | *1 (5.3%)       | 0 (0.0%)                                       | 0 (0.0%)        | 0 (0.0%)        | 1 (1.7%)        |
| Muscle ache  | 0 (0.0%)                                       | 1 (4.8%)        | 2 (9.5%)                                       | 1 (5.3%)        | 0 (0.0%)                                       | 0 (0.0%)        | 2 (3.3%)        | 2 (3.3%)        |
| Fatigue (malaise/lethargy)   | 1 (5.3%)                                       | 3 (14.3%)       | 3 (14.3%)                                      | 1 (5.3%)        | 0 (0.0%)                                       | 1 (5.0%)        | 4 (6.7%)        | 5 (8.3%)        |
| Runny/stuffy nose  | 3 (15.8%)                                      | 5 (23.8%)       | 12 (57.1%)                                     | 11 (57.9%)      | 8 (40.0%)                                      | 8 (40.0%)       | 23 (38.3%)      | 24 (40.0%)      |
| Cough  | 1 (5.3%)                                       | 4 (19.0%)       | 6 (28.6%)                                      | 8 (42.1%)       | 10 (50.0%)                                     | 7 (35.0%)       | 17 (28.3%)      | 19 (31.7%)      |
| Headache   | 3 (15.8%)                                      | 6 (28.6%)       | 4 (19.0%)                                      | 4 (21.1%)       | 2 (10.0%)                                      | 2 (10.0%)       | 9 (15.0%)       | 12 (20.0%)      |
| Chills   | 0 (0.0%)                                       | 3 (14.3%)       | 2 (9.5%)                                       | 1 (5.3%)        | 0 (0.0%)                                       | 0 (0.0%)        | 2 (3.3%)        | 4 (6.7%)        |
| Acute change in feeding/appetite requiring a visit to a health care provider | 1 (5.3%)                                       | 3 (14.3%)       | 2 (9.5%)                                       | 1 (5.3%)        | 1 (5.0%)                                       | 1 (5.0%)        | 4 (6.7%)        | 5 (8.3%)        |
| Bloody nose  | 0 (0.0%)                                       | 0 (0.0%)        | 0 (0.0%)                                       | 1 (5.3%)        | 2 (10.0%)                                      | 0 (0.0%)        | 2 (3.3%)        | 1 (1.7%)        |
| Hoarseness/laryngitis  | 0 (0.0%)                                       | 0 (0.0%)        | 1 (4.8%)                                       | 2 (10.5%)       | 0 (0.0%)                                       | 0 (0.0%)        | 1 (1.7%)        | 2 (3.3%)        |

SE indicates solicited events; TCID<sub>50</sub>, median tissue culture infectious dose; N, number in population; n, observed number.

\*Event not based on medical evaluation by a healthcare provider.

<sup>†</sup>Sore throat was reported more frequently in the 10<sup>5</sup> and 10<sup>6</sup> TCID<sub>50</sub> groups of MEDI-534 than in the corresponding placebo groups, but all events were mild/moderate, occurred between 0-25 days after vaccination, and were not associated with viral shedding.

**Immunogenicity.** MEDI-534 was minimally immunogenic in this seropositive pediatric population (Table, Supplemental Digital Content 1, <http://links.lww.com/A1121>). A ≥4-fold increase from baseline serum RSV titers was reported for one subject (predose 15; postdose 320) in the 10<sup>4</sup> TCID<sub>50</sub> MEDI-534 group (who also had a ≥4-fold increase from baseline serum hPIV3 titers) and one subject in the 10<sup>6</sup> TCID<sub>50</sub> MEDI-534 group (predose 10; postdose 640). Another subject in the 10<sup>6</sup> TCID<sub>50</sub> MEDI-534 group who was found to shed wild-type RSV only on day 3 seroresponded (predose 40; postdose 160). A ≥4-fold increase from baseline serum hPIV3 titers was reported for one subject (predose 8; postdose 32) in the 10<sup>4</sup> (same subject mentioned earlier) and 10<sup>6</sup> TCID<sub>50</sub> MEDI-534 groups (predose 32; postdose 256), and 2 subjects in the placebo group (predose 32 and 128; postdose 256 and 1024, respectively).

**Vaccine Viral Shedding.** No subjects receiving MEDI-534 shed vaccine-like virus.

### DISCUSSION

A number of RSV and PIV3 vaccine candidates have been evaluated over the past 40 years with intranasal administration emerging as the preferred administration route because it provides local and systemic protection against infection, and is not associated with enhanced RSV disease.<sup>2,6</sup> MEDI-534, a live, attenuated vaccine against RSV and PIV3, demonstrated an acceptable safety profile in animal models, and in human adults with doses up to 10<sup>6</sup> TCID<sub>50</sub>.<sup>8-10</sup> In this study, MEDI-534 was administered for the first time to RSV/PIV3 seropositive 1 to 9-year-old children. Individual SEs occurred sporadically throughout the observation period, and no temporal pattern or clustering could be attributed to vaccination. The most frequently reported SEs in the MEDI-534 group were signs and symptoms associated with common child-

hood illnesses that included runny/stuffy nose, cough, sore throat, headache, and mild fever. These SEs were reported at similar frequencies in the placebo group.

Individual events of sore throat, epistaxis, and otitis media were numerically higher in some of the dosage groups. Because of the small sample size, and lack of association with vaccine shedding, causality of these events cannot be ascribed definitively to vaccination. In addition, the cohorts were enrolled in different geographical locations and were vaccinated at different times of the year, confounding intercohort comparisons. In summary, MEDI-534 demonstrated an acceptable safety profile in RSV/hPIV3 seropositive children. As expected, on the basis of the adult phase-I data and prior studies with live RSV and PIV3 vaccines, MEDI-534 had restricted replication and was minimally immunogenic in seropositive children. A safe and immunogenic dosage level for seronegative infants, who are the target population for this vaccine, is not possible to derive from data in seropositive children. Therefore, based on these findings, continued evaluation in a dose escalation/age de-escalation study in seronegative infants, with further evaluation of the safety profile of the vaccine is planned.

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## REFERENCES

- Lee MS, Walker RE, Mendelman PM. Medical burden of respiratory syncytial virus and parainfluenza virus type 3 infection among US children. Implications for design of vaccine trials. *Hum Vaccine*. 2005;1:6–11.
- Wright PF, Karron RA, Belshe RB, et al. The absence of enhanced disease with wild type respiratory syncytial virus infection occurring after receipt of live, attenuated, respiratory syncytial virus vaccines. *Vaccine*. 2007;25:7372–7378.
- Karron RA, Wright PF, Newman FK, et al. A live human parainfluenza type 3 virus vaccine is attenuated and immunogenic in healthy infants and children. *Infect Dis*. 1995;172:1445–1450.
- Karron RA, Belshe RB, Wright PF, et al. A live human parainfluenza type 3 virus vaccine is attenuated and immunogenic in young infants. *Pediatr Infect Dis J*. 2003;22:394–405.
- Belshe RB, Newman FK, Tsai TF, et al. Phase-2 evaluation of parainfluenza type 3 cold passage mutant 45 live attenuated vaccine in healthy children 6 to 18 months old. *J Infect Dis*. 2004;189:462–470.
- Murphy BR, Collins PL. Live-attenuated virus vaccines for respiratory syncytial and parainfluenza viruses: applications of reverse genetics. *J Clin Invest*. 2002;110:21–27.
- Haller AA, Miller T, Mitiku M, et al. Expression of the surface glycoproteins of human parainfluenza virus type 3 by bovine parainfluenza virus type 3, a novel attenuated virus vaccine vector. *J Virol*. 2000;74:11626–11635.
- Tang RS, Schickli JH, MacPhail M, et al. Effects of human metapneumovirus and respiratory syncytial virus antigen insertion in two 3' proximal genome positions of bovine/human parainfluenza virus type 3 on virus replication and immunogenicity. *J Virol*. 2003;77:10819–10828.
- Tang RS, MacPhail M, Schickli JH, et al. Parainfluenza virus type 3 expressing the native or soluble fusion (F) Protein of Respiratory Syncytial Virus (RSV) confers protection from RSV infection in African green monkeys. *J Virol*. 2004;78:11198–11207.
- Tang RS, Spaete RR, Thompson MW, et al. Development of a PIV-vectored RSV vaccine: Preclinical evaluation of safety, toxicity, and enhanced disease and initial clinical testing in healthy adults. *Vaccine*. 2008;26:6373–6382.

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Interferon gamma receptor (IFN- $\gamma$ R) deficiencies are rare autosomal recessive or dominant inherited disorders. To date, autosomal recessive complete IFN- $\gamma$ R1 deficiency has been diagnosed in 27 patients (23 kindreds) from 16 countries, and is associated with early-onset and recurrent disseminated mycobacterial infections.<sup>1–3</sup> Twenty-one mutations have been identified causing either a lack of IFN- $\gamma$ R1 expression or an expression of nonfunctional receptors, both leading to cellular unresponsiveness to IFN.<sup>1</sup>

The prognosis of complete IFN- $\gamma$ R1 deficiency is poor with <20% surviving to 12 years of age.<sup>3</sup> Recently, a patient reached 19 years of age, but with severe repeated mycobacterial illnesses.<sup>4</sup> Treatment with exogenous IFN- $\gamma$  has no effect in the absence of functional receptors and antibiotics, although given continuously, can only delay the progression of mycobacterial infections. Hematopoietic stem cell transplantation (HSCT) is the only curative treatment, and until now, 9 patients have received 12 HSCTs, all from family donors.<sup>5–8</sup> Four patients died within 8 months of transplantation, 2 survived despite of autologous reconstruction, and in 3 children, HSCT has been curative.<sup>5,7,8</sup> A major problem has been the high rate of graft rejection, recently explained by the high levels of circulating IFN- $\gamma$ ,<sup>9</sup> at least in the mouse model.<sup>10</sup>

## CASE REPORT

Our patient is a 9-year-old girl of Finnish descent. BCG vaccination as newborn caused severe inguinal lymphadenitis, treated by surgery and for 6 months by INH, rifampin, and ethambutol.

At 7 years of age, the patient developed hip and leg pain, weight loss, fatigue, fever, and respiratory distress. Nonspecific inflammatory markers increased progressively, but the blood counts (hemoglobin, platelets, and white blood cells, with differential) were normal. There was pulmonary infiltration and pleural fluid in chest radiograph, an enlarged spleen with multiple lesions in ultra-sound, mediastinal mass in computed tomography (CT), and pelvic and femoral bone lesions in magnetic resonance imaging (MRI). Histologic samples from bone, lung, and mediastinum showed nonspecific inflammation. Histochemical staining showed acid-fast bacilli, but there was no granulomatous reaction. *Mycobacterium avium intracellulare* was cultured from bone, lung, pleural, and mediastinal samples, and grew in 3 blood cultures.

In the immunologic studies, no evidence of immune deficiency was found. Blood lymphocytes, their subpopulations, T cell responses to mitogens, and serum immunoglobulins were normal.

Therapy was started with 5 antibiotics, and when the results of the susceptibility tests were available, continued with ethambutol, rifabutin, and clarithromycin. IFN- $\gamma$  injections were started since the clinical presentation was suggestive for IFN- $\gamma$  axis disorder. The patient responded well to antibiotics, and after 3 months, there were no major subjective symptoms.

In cell cultures, the function of the IFN- $\gamma$ -interleukin-12(IL-12) axis was impaired.<sup>11</sup> No IL-12p70 secretion was observed in response to BCG or BCG+IFN- $\gamma$ . However, the secretion of IFN- $\gamma$  in response to BCG and BCG+IL-12 was normal, and IFN- $\gamma$  concentration in plasma was elevated (370 pg/mL). Thus, the patient was able to produce IFN- $\gamma$ , but was suspicious of IFN- $\gamma$  receptor deficiency. Results of the studies on her parents and the healthy brother were normal.

## SUCCESSFUL HEMATOPOIETIC STEM CELL TRANSPLANTATION FROM AN UNRELATED DONOR IN A CHILD WITH INTERFERON GAMMA RECEPTOR DEFICIENCY

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**Abstract:** Interferon gamma receptor deficiency is a rare autosomal recessive inherited disorder, with poor prognosis due to early-onset, recurrent, and disseminated mycobacterial infections. Hematopoietic stem cell transplantation (HSCT), the only curative treatment, is particularly difficult in these patients owing to a high rate of graft rejection. We report the first successful hematopoietic stem cell transplantation with an unrelated donor, performed in a schoolgirl with severe interferon gamma receptor 1 deficiency caused by a novel mutation.

**Key Words:** atypical mycobacterial disease, graft versus host disease, interferon gamma receptor deficiency, hematopoietic stem cell transplantation

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