

Letter to the Editor

Safety and efficacy of measles, mumps, and rubella vaccine in patients with DiGeorge syndrome

To the Editor:

DiGeorge syndrome is the most common cause of T-cell lymphocytopenia in infants, affecting 1 in 3000 children. More than 90% of these patients have a microdeletion in 22q11.2 chromosome, which can cause an array of clinical features, including cardiac and neurologic anomalies in addition to an underdeveloped thymus gland.

Most patients with 22q11.2 microdeletion have reduced numbers of circulating T cells that gradually increase with time, frequently providing these patients with adequate protection from infections. One of the critical questions in the management of 22q11.2 microdeletion is the safety and efficacy of live vaccines in view of their immunodeficiency.¹

Infections with measles, mumps, and rubella (MMR) viruses can be prevented effectively by immunization with MMR vaccine. Recent severe outbreaks of these viruses in unimmunized subjects prompted the practice to immunize even patients with HIV infection. Little is known about the safety and long-term efficacy of MMR vaccine in patients with 22q11.2 microdeletion.²

We studied the safety of MMR vaccine given to 82 patients with 22q11.2 microdeletion by the investigators (40 patients defined as group A) or by primary physicians (42 patients defined as group B). Adverse reactions typically occur within 10 to 14 days after MMR vaccine. However, to ensure that even remote effects associated with impaired immune function in patients with 22q11.2 microdeletion were accounted for, we considered all events that occurred within 60 days of vaccination. Mild reactions were defined as fever and self-limited skin rash, which did not require medical intervention. Moderate-to-severe reactions included arthritis, thrombocytopenia or disseminated MMR, hospitalization, life-threatening allergic reactions, or death. Adverse events or complications associated with the vaccine were assessed by means of telephone interview in the 40 patients of group A and during clinic visits in the 42 patients of group B. Mild reactions occurred in 6 (7.3%) of 82 patients, but moderate or severe reactions were not observed. These results indicate that MMR vaccination was safe in the patients studied. This is in sharp contrast to a previous questionnaire-based survey³ that showed a higher reaction frequency but in keeping with the 5% rate observed in the general population.⁴ Immune function was evaluated immediately before the administration of the MMR vaccine in the 40 patients of group A. Flow cytometry demonstrated that 1 patient had 457 cells/mm³, whereas all other patients had greater than 500 circulating CD4⁺ cells/mm³ (Fig 1). Circulating CD8⁺ lymphocytes were normal in all but 1 patient. Mitogenic responses to PHA were normal (>75% of healthy control responses) in 31 patients and somewhat reduced (50% to 75% of healthy control responses) in 9 patients.

Further studies are required to determine the safety of live viral vaccines among patients with DiGeorge syndrome caused by 10P or CHD7 mutations that were excluded from this study. Also, our study was not designed to determine the threshold number or function of T cells, which allows safe administration of the

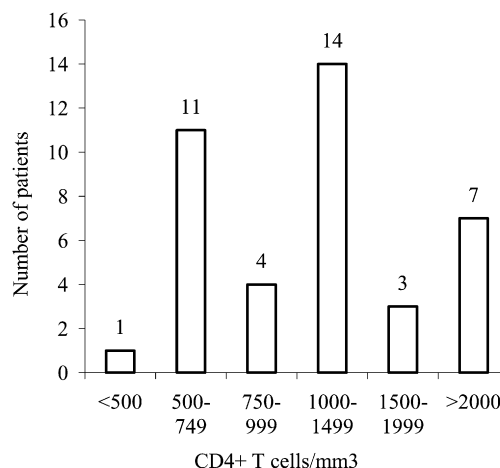


FIG 1. Distribution of CD4⁺ T cells in 40 patients with DiGeorge syndrome to MMR vaccination. The number of patients in each category is provided above the appropriate bar.

vaccine. Few patients with less than 500 CD4⁺ cells/mm³ have been studied thus far in this or previous studies.⁵⁻⁷

We next used the Euroimmun ELISA (Euroimmun, Lübeck, Germany) to test the ability to mount and sustain a protective antibody response to measles (>200 mIU/mL), mumps (>20 RU/mL), and rubella (>10 RU/mL) in the 42 patients of group B. The patients' ages ranged from 2 to 19 years (median, 5.5 years). At the time of assessment, all patients had normal serum immunoglobulin levels, robust levels of tetanus antibody, and normal numbers of circulating B cells. Additionally, mitogenic responses to PHA, which were available for 40 of 42 patients in group B, were normal in 35 patients and somewhat reduced (50% to 75% of healthy control responses) in 5 patients. Antibodies were assessed 0.5 to 16 years (median, 3.0 years) after MMR vaccination. As a control group, we studied 110 age-matched healthy children who were 0.5 to 14 years (median, 3.0 years) of age after 2 MMR vaccine doses. In agreement with previous reports, there were no significant differences in seroconversion after 1 or 2 MMR vaccine doses. Within group B, protective MMR antibody levels were documented in 11 (84.6%) of 13 patients tested within 1 year after vaccination, demonstrating robust seroconversion to MMR, which is similar to previous reports.^{5,6} In contrast, only 10 (34.5%) of 29 patients who were tested 2 or more years after vaccination had protective antibodies to MMR, which was significantly lower ($P < .001$) than in patients within the first year after vaccination or in healthy control subjects, among whom 96 (87.2%) of 110 had protective antibodies to MMR. Although we did not serially measure antibody levels in the same patient cohort, the results of our study suggest that although patients with 22q11 microdeletion have robust seroconversion to MMR vaccine, they have difficulty in sustaining long-term protective antibodies. Similar losses of MMR antibodies have been documented in patients with HIV and in immune-suppressed subjects after organ transplantation, suggesting that T cells are required for induction of long-term immune memory and sustained production of antibodies to MMR.^{8,9} Indeed, among 7 of the 22q11 microdeletion patients with less than

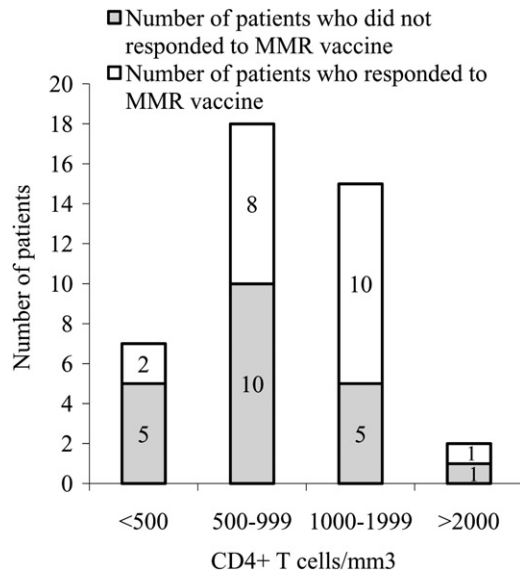


FIG 2. Distribution of CD4⁺ T cells in 40 patients with 22q11 microdeletion at the time of MMR antibody assessment.

500 CD4⁺ cells/mm³, 5 patients did not have antibodies to MMR compared with only 16 patients who did not have antibodies to MMR among the 35 patients with 500 or more CD4⁺ cells/mm³ (Fig 2); however, this difference was not statistically significant ($P = .205$, Fisher exact test).

In summary, we have demonstrated here that MMR vaccination is safe in patients with 22q11.2 microdeletion who have at least near or more than 500 circulating CD4⁺ cells/mm³. However, sustaining long-term protective MMR antibody levels, even after repeat vaccination, appear far lower than those in age-matched control subjects. On the basis of this study, we propose that patients with 22q11.2 microdeletion should be periodically assessed for antibody levels and reimmunized accordingly.

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