

## LETTER

## Immunogenicity and safety profile of the monovalent A/H1N1 MF59-adjuvanted vaccine in patients affected by cystic fibrosis

Viral respiratory tract infections may determine lung function deterioration in patients affected by cystic fibrosis (CF). Viruses may have a synergistic action with bacteria to damage the respiratory tract; they may also promote airway bacterial colonisation.<sup>1</sup> Influenza virus infection has been described to increase the number of CF pulmonary exacerbations and the incidence of hospitalisation.<sup>2</sup> For this reason, vaccination is strongly recommended annually. The immunogenic effect and safety of influenza vaccines in CF children are comparable with that of healthy individuals.<sup>3</sup> The reported adverse events after vaccination are mild and not persisting. In 2009, a novel swine pandemic influenza A virus (A/H1N1) was identified. To date, the outcome of H1N1 infection has been described only in CF adults,<sup>4</sup> and no data are available about the safety and immunogenicity of the A/H1N1 vaccine administered to CF patients. The aim of our study was to evaluate safety and immunogenicity of the monovalent A/H1N1 MF59-adjuvanted surface antigen vaccine administered to CF patients. All CF patients aged 6 months to 26 years and followed at the referral Centre of the Bambino Gesù Children's Hospital (Rome, Italy) were assessed for eligibility. Exclusion criteria were a contraindication for the influenza vaccine or a previous documented H1N1 virus infection. All subjects received one dose of Focetria (Novartis) monovalent inactivated pandemic influenza vaccine corresponding to 7.5 µg of haemagglutinin (HA) antigen strain A/California/7/2009 (H1N1)v like strain (X-179A) MF59-adjuvanted between November 2009 and February 2010. The vaccine was administered intramuscularly into the deltoid muscle of the non-dominant arm on day 0. Blood samples were collected on day 0 and on day 21 to assess immunogenicity according to the Committee for Proprietary Medicinal Products (CPMP) criteria<sup>5</sup>; CD4 T cell counts were also assessed on day 0 to exclude immunodeficiency. Patients or their parents recorded in a diary card the onset and severity of solicited local and systemic reactions within 7 days after the vaccine administration.

We enrolled 48 CF patients with an average good pulmonary function and nutritional status. They showed normal CD4 T cell counts. All patients were assessed for safety and 33 of them for immunogenicity. There were no dropouts because of adverse reactions. The vaccine was well tolerated and

**Table 1** Demographics, immunogenicity and safety data of the study group

| Demographics                                   |               | Nutritional status         |                                 |
|--|---------------|----------------------------|---------------------------------|
| Patients enrolled: 48                          |               |                            |                                 |
| Mean age: 14.4 years (range 8 months–26 years) |               |                            |                                 |
| M/F: 20/28                                     |               | Patients <18 years (n=32): | mean HAP 25.1                   |
| F508del (37/48, 77.1%):                        |               |                            | mean WAP 41.8                   |
| 8 homozygotes                                  |               |                            |                                 |
| 29 heterozygotes                               |               |                            |                                 |
| Pseudomonas colonisation: 29/48 (60.4%)        |               | Patients ≥18 yrs (n=16):   | mean BMI 21.9                   |
| Mean FEV <sub>1</sub> : 86.5% ± 25.1           |               |                            |                                 |
| O <sub>2</sub> therapy: 1 patient              |               |                            |                                 |
| Immunogenicity*                                |               |                            |                                 |
| Patients assessed: 33                          |               | <b>Baseline</b>            | <b>21 days postimmunisation</b> |
| CD4 T cell/µl (%)                              |               | 1163 (42.3)                | —                               |
| Geometric mean titre (95% CI)                  |               | 40 (20–81)                 | 582 (388–872)                   |
| Geometric mean ratio of HI titre (95% CI)      |               | —                          | 13.9 (6.9–26.7)                 |
| % Seroconversion (95% CI)                      |               | —                          | 83 (60–91)                      |
| Safety   |               |                            |                                 |
| <b>Local reactions:</b>                        | 13/48 (27.1%) | Pain                       | 12/48 (25%)                     |
|  |               | Swelling/redness           | 7/48 (14.6%)                    |
| <b>Systemic reactions:</b>                     | 12/48 (25%)   | Fever                      | 5/48 (10.4%)                    |
|  |               | Myalgia                    | 4/48 (8.3%)                     |
|  |               | Headache                   | 3/48 (6.3%)                     |
|  |               | Fatigue                    | 3/48 (6.3%)                     |
|  |               | Chills                     | 1/48 (2.1%)                     |

\*Immunogenicity was assessed according to the CPMP criteria: seroconversion was defined as prevaccination antibody titre of 1:10 or less and a postvaccination titer of 1:40 or more or a prevaccination titre greater than 1:10 and an increase in the antibody titre by a factor of four or more. Seroconversion rate was calculated as the percentage of patients that displayed seroconversion. Serum antibody titres were determined using the haemagglutination inhibition (HI) assay. Sera geometric mean titres (GMT) and ratios (as fold increase) in HI titres of day 21 to day 0 titres were also calculated.

HAP, height for age percentile; WAP, weight for age percentile; BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in 1 s.

no serious adverse events have been reported. All recorded symptoms were mild and short-lasting. The most frequent reported symptoms were local reactions. Seroconversion rate was satisfactory and met all the CPMP criteria. Demographics, immunogenicity and safety data are shown in table 1.

In conclusion, a single 7.5 µg dose of the monovalent A/H1N1 MF59-adjuvanted vaccine results in a high rate of seroconversion in CF patients. These data support the current influenza vaccination strategy. The vaccine is well tolerated and the frequency of adverse events is comparable with literature data regarding other influenza vaccines. However, we studied a small cohort of young patients with an overall good nutritional and lung status. In severe malnourished CF patients, supposed to have a decreased immune response, the vaccine may not have the same efficacy. Future prospectual studies are needed to evaluate the benefits of influenza vaccines on defined clinical outcomes.

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