LETTERS

Clinical outcomes of pandemic (H1N1) 2009 influenza (swine flu) in adults with cystic fibrosis

Patients with cystic fibrosis (CF) suffer recurrent bacterial pulmonary infections, but viral infections can also cause acute clinical deterioration.[1] Certain patient groups suffer increased morbidity following pandemic (H1N1) 2009 influenza (swine flu),[2] but there are few previous reports of outcomes in individuals with CF.[3 4] The West Midlands, along with Greater London, has had the highest incidence of H1N1 influenza in the UK.[5] We therefore examined the outcomes of patients diagnosed with H1N1 influenza at the West Midlands Adult CF Centre.

From June 2009 to April 2010 all adults with CF at our regional centre with potential H1N1 influenza had nasopharyngeal swabs tested by PCR. PCR testing was instituted in patients with fever >38°C together with one or more of the following: sore throat, rhinorrhoea, loose bowel motions, myalgia and headache. We documented clinical management, as well as lung function and body mass index (BMI) at the visit prior to their febrile illness and at their subsequent clinic visit. We used paired and unpaired Student t test and Mann–Whitney U test as indicated.

Out of our total patient population of 325 adults with CF, 45 patients had nasopharyngeal swabs tested by PCR over the study period. Thirteen patients (4% of our patient population) tested positive ('H1N1 +ve' group) and 32 patients (9.8%) tested negative for H1N1 influenza ('H1N1 −ve group'). In three of the 'H1N1 −ve' group, PCR was positive for alternative viruses (1 adenovirus, 1 parainfluenza type 4, and 1 herpes simplex type 1).

There were no statistically significant differences in baseline clinical characteristics between the two groups (table 1). Presenting symptoms in the 'H1N1 +ve' group were: fever >38°C (13/13 patients), increased sputum production (13/13), sore throat (8/13), myalgia (5/13), nausea/vomiting (5/13) and headache (2/13). Fever, increased sputum production, nausea/vomiting and headaches were similarly common in the 'H1N1 −ve group'; however, none of the patients in the 'H1N1 −ve group complained of sore throat or myalgia. Blood test results showed a trend towards lower total white cell count and C-reactive protein (CRP) in the 'H1N1 +ve' group compared with the 'H1N1 −ve' group. All patients initially received antibiotics and oseltamivir, and in 'H1N1 +ve' patients oseltamivir was continued for a median of 10 days. Nine of the 13 patients in the 'H1N1 +ve group' required hospital admission, but there were no differences in duration of hospital admission or requirement for antibiotics between the two groups. There were no statistically significant differences in clinical outcomes between the 'H1N1 +ve' and 'H1N1 −ve' groups. In both the 'H1N1 +ve' and 'H1N1 −ve' groups there was a non-significant decrease in FEV_1 (forced expiratory volume in 1 s) % predicted, FVC (forced vital capacity) % predicted (table 1) and BMI. None of the patients in the 'H1N1 +ve' group had new changes on their chest radiograph or required ventilatory support.

In our experience, adults with CF have generally experienced a relatively mild illness as a result of the first influenza pandemic of the 21st century. However, the CF community is well aware of the potential implications of a subsequent more virulent pandemic in future years.

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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.[1] Influenza virus infection has been described to increase the number of CF pulmonary exacerbations and the incidence of hospitalisation.[2] 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.[3] 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,[4] 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

Table 1 Patient characteristics and lung function data

	Age, median (range)	Male, n (%)	Chronic *Pseudomonas* airway infection, n (%)	CF-related diabetes, n (%)	CF liver disease, n (%)	Transplant recipient, n (%)	FEV_1 % predicted prior to presenting illness, mean±SD	FEV_1 % predicted following presenting illness, mean±SD	FVC % predicted prior to presenting illness, mean±SD	FVC % predicted following presenting illness, mean±SD
'H1N1 +ve' group (n=13)	22 (17–48) years	6 (46.2%)	13 (100%)	7 (53.8%)	6 (46.2%)	3 (23.1%)	51.4±18.3%	46.5±16.7%	67.4±17.9%	64.0±19.9%
'H1N1 −ve' group (n=32)	26 (15–59) years	15 (46.9%)	31 (96.9%)	24 (75%)	6 (18.8%)	3 (9.4%)	50.7±20.9%	49.8±19.5%	66.4±23.4%	65.0±20.9%

CF, cystic fibrosis; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

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%):	8 homozygotes		mean WAP 41.8
	29 heterozygotes		
Pseudomonas colonisation: 29/48 (60.4%)		Patients≥18 yrs (n=16):	mean BMI 21.9
Mean FEV_1: 86.5%±25.1			
O_2 therapy: 1 patient			

Immunogenicity*	**Baseline**	**21 days postimmunisation**
Patients assessed: 33		
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			
Local reactions:	13/48 (27.1%)	Pain	12/48 (25%)
		Swelling/redness	7/48 (14.6%)
Systemic reactions:	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_1, forced expiratory volume in 1 s.

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[5]; 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 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 prospectical studies are needed to evaluate the benefits of influenza vaccines on defined clinical outcomes.

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Influenza A/H1N1 in patients with cystic fibrosis in Italy: a multicentre cohort study

The clinical consequences of influenza are severe in cystic fibrosis (CF), but the impact of A/H1N1 virus infection remains poorly defined.[1 2] Pandemic influenza A/H1N1 started in Italy in September 2009 and CF patients were included among those at risk of complications and recommended to receive A/H1N1 vaccine. Better characterisation of the impact of influenza A/H1N1 in comparison with other flu-like illnesses in CF would provide a rational basis for antiviral treatment and vaccination strategies for the next flu season.

Within the Italian Cystic Fibrosis Society, we sent a questionnaire to 30 centres to collect follow-up data for all patients with influenza-like symptoms consecutively seen between November 2009 and March 2010. Realtime RTPCR test was performed to define A/H1N1 status.[3] Continuous variables are reported as medians, IQR (see online supplement for details of study methods).

Nineteen centres reported data from 127 patients: 68 were 'A/H1N1+ve' and 59 were 'A/H1N1–ve' for the RT-PCR test.

Symptom onset peaked during calendar week 45 in A/H1N1+ve patients, similar to the general Italian population,[4] whereas A/H1N1–ve patients showed a bimodal incidence peak at weeks 45 and 47 (online supplementary figure S1).

A/H1N1+ve patients tended to be younger than A/H1N1–ve patients (40% vs 58% aged ≥18 years; p=0.051), with no other differences in clinical characteristics or symptoms leading to presentation to centres (online supplementary table S1).