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Prognosis of hospitalized patients with 2009 H1N1 influenza in Spain: influence of neuraminidase inhibitors

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Background: The H1N1 influenza pandemic strain has been associated with a poor prognosis in hospitalized patients. The present report evaluates the factors influencing prognosis.

Methods: A total of 813 patients hospitalized with H1N1 influenza in 36 hospitals (nationwide) in Spain were analysed. Detailed histories of variables preceding hospital admission were obtained by interview, validating data on medications and vaccine with their attending physicians. Data on treatment and complications during hospital stay were recorded. As definition of poor outcome, the endpoints of death and admission to intensive care were combined; and as a further outcome, length of stay was used.

Results: The mean age was 38.5 years (SD 22.8 years). There were 10 deaths and 79 admissions to intensive care (combined, 88). The use of neuraminidase inhibitors was reported by 495 patients (60.9%). The variables significantly associated with a poor outcome were diabetes (OR=2.21, 95% CI=1.21–4.02), corticosteroid therapy (OR=3.37, 95% CI=1.39–8.20) and use of histamine-2 receptor antagonists (OR=2.68, 95% CI=1.14–6.36), while the use of neuraminidase inhibitors (OR=0.57, 95% CI=0.34–0.94) was protective. Neuraminidase inhibitors within the first 2 days after the influenza onset reduced hospital stay by a mean of 1.9 days (95% CI=4.7–6.6).

Conclusions: The use of neuraminidase inhibitors decreases the length of hospital stay and admission to intensive care and/or death.

Keywords: prevention, adverse outcomes, length of stay, flu, pandemic

Introduction

Influenza A pandemic H1N1 2009 virus infections began to spread in Spain during spring 2009. Reports suggested high mortality in children and adults associated with the new virus in Mexico[1,2] and Argentina,[3] as well as in previously healthy young people. Analysis of cases hospitalized in the USA showed a mortality rate of 7%, with 25% of patients being

admitted to the intensive care unit (ICU).[4] A study of 32 patients infected with the pandemic virus strain admitted to Spanish ICUs found a mortality rate of 25%, somewhat lower than in Latin American countries.[5] These findings suggest that the H1N1 virus is more virulent than previous strains.

As there was no specific targeted vaccine giving protection against the H1N1 influenza virus available at the beginning of the outbreak, health authorities began to recommend administration of neuraminidase inhibitors to reduce transmission and/or complications. Various studies have suggested that these drugs are also effective in reducing the severity of the infection.[4,6,7]

We reviewed nationwide Spanish data on hospitalized patients with 2009 H1N1 influenza A in order to: (i) evaluate the frequency of adverse outcomes during hospitalization; and (ii) identify the factors influencing poor/good outcome, including the use of neuraminidase inhibitors shortly after the onset of symptoms.

Methods

Study design

We carried out a multicentre study in 36 hospitals from seven Spanish regions (Andalusia, Catalonia, Castile and Leon, Madrid, Navarre, the Basque Country and Valencia). Between July 2009 and February 2010 we selected hospitalized patients with influenza syndrome, acute respiratory infection, septic shock or multiple organ failure in whom influenza virus A (H1N1) 2009 infection was confirmed by real-time reverse-transcription PCR (RT-PCR) from nasopharyngeal swabs; haemagglutinin (HA) sequencing was performed. We excluded patients who had nosocomial infection, defined as pandemic virus infection in a patient that appears ≥48 h after admission for another cause. All information collected was treated as confidential, in strict observance of legislation for observational studies. The study was approved by the Ethics Committees of the hospitals involved, following the Declaration of Helsinki principles. Written informed consent was obtained from all patients included in the study.

Selection of patients

During the pandemic flu all patients suspected of having the disease, either in outpatient clinics or hospitals, were diagnosed by RT-PCR of samples from nasopharyngeal swabs. Within the next 48 h, hospitalized patients were interviewed at the centre. Of these, 23 rejected participation and 12 were excluded because flu had been acquired after hospital admission.

Data collection

The following demographic variables and pre-existing medical conditions were recorded for all study participants: age, sex, ethnicity, educational level, smoking, alcoholism, pregnancy in women aged 15–49 years, history of pneumonia in the previous two years, chronic obstructive pulmonary disease (COPD), asthma, cardiovascular disease, renal failure, diabetes, HIV infection, disabling neurological disease, cancer, transplantation, morbid obesity (body mass index ≥40), use of neuraminidase inhibitors before hospital admission (and their timing relative to the onset of symptoms, verified after contacting the prescribing general practitioner), use of other medications in the 90 days before hospital admission (corticosteroids, antibiotics etc.) and treatment received during hospitalization (medications, catheters and mechanical ventilation). For each vaccine, a case was considered vaccinated if the vaccine had been received ≥14 days before the onset of symptoms. Data were collected during hospital admission and the clinical chart was also reviewed after discharge.

The outcome variables were admission to an ICU, in-hospital death and length of hospital stay (in days). Given that the number of deaths was very low, a combined endpoint was classified as 'poor outcome': ICU admission and/or in-hospital death.

Statistical analysis

Bivariate comparisons were made using Pearson's χ^2 test for categorical variables and Student's *t*-test for continuous variables. As a measure of association, the relative risk (OR) and 95% CI were calculated. Logistic regression was applied in the multivariate analysis for dichotomous adverse outcomes. To determine the variables to be included in the multivariate analysis, the procedure described by Sun *et al*.[8] was followed. Intermediate variables were discarded. We ran two stepwise models, one backward and another forward, including variables with $P<0.2$.[9,10] We constructed a list of predictors of mortality identified in other studies. Using information from stepwise models and the list of predictors, a saturated model was built, and by using a heuristic approach, variables that did not change the coefficient of the bundles by more than 10% were discarded, in order to construct a parsimonious model retaining all important confounders.

To analyse the impact of different variables on the length of hospital stay, patients who died were excluded from these analyses. Given that hospital stay did not follow the normal curve, natural logarithms were used. Firstly, to select potential variables related to length of stay, we used Cox regression in the same fashion as described above for the logistic regression analysis. The variables selected by this model were tested by including other potential candidates according to the logistic regression analyses. Secondly, an analysis of covariance was applied to estimate the adjusted means of hospital length of stay. All analyses were made using the Stata 10/SE package (College Station, TX, USA).

Results

There were a total of 813 patients [410 (50.4%) were female, of which 51 (12%) were pregnant]. The mean age was 38.5 years (SD 22.8) and 24% were aged <18 years. The use of neuraminidase inhibitors was reported by 495 patients (60.9%), with oseltamivir being administered in all cases but two (zanamivir). During hospitalization, 79 patients (9.7%) were admitted to the ICU and 10 died (1.2%), of whom 9 were not receiving intensive care. No death occurred in pregnant women, of whom only one was admitted to the ICU. The timings of the use of neuraminidase inhibitors before hospital admission were: 332 patients in the first 24 h after the onset of symptoms, 97 between 24–48 h and 66 after 48 h (Table 1).

The relationship between study variables and ICU admission/in-hospital death is shown in Table 2. In the univariate analyses, age, most comorbidities (COPD, diabetes, liver failure and cardiovascular disease), ex-smoking, corticosteroid therapy and histamine-2 receptor antagonists were associated with an adverse outcome during hospitalization. In the multivariate models, the variables significantly associated with a poor outcome were diabetes (OR=2.21, 95% CI=1.21–4.02), corticosteroid therapy (OR=3.37, 95% CI=1.39–8.20) and use of histamine-2 receptor antagonists (OR=2.68, 95% CI=1.14–6.36). Use of neuraminidase inhibitors was protective (OR=0.57, 95% CI=0.34–0.94). Pneumonia at admission, COPD, ex-smoking and liver failure showed a trend to association.

Table 1. Description of the study population ($N=813$)

Variable	
Sex (female), *n* (%)	410 (50.4)
pregnant, *n* (%)	51 (12.4)
Age	
mean (SD)	38.5 (22.8)
median, IQR	41 (19–55)
≤18 years, *n* (%)	195 (24.0)
19–45, *n* (%)	275 (33.8)
46–65, *n* (%)	242 (29.8)
>65, *n* (%)	101 (12.4)
Race (Caucasian), *n* (%)	708 (87.1)
Vaccinated with pandemic H1N1 vaccine, *n* (%)	13 (1.6)
Vaccinated with seasonal influenza vaccine, *n* (%)	155 (19.1)
Smoking, *n* (%)	
current	178 (21.9)
ex-smoker	128 (15.7)
Alcoholism, *n* (%)	44 (5.4)
Corticosteroid therapy, *n* (%)	31 (3.8)
COPD, *n* (%)	76 (9.4)
Number of comorbidities, n (%)	
0	242 (29.8)
1	195 (24.0)
2–3	212 (26.1)
≥4	164 (20.2)
Use of neuraminidase inhibitors before admission, *n* (%)	495 (60.9)
Admission to ICU, *n* (%)	79 (9.7)
In-hospital death, *n* (%)	10 (1.2)
Length of hospital stay (days), mean (median, IQR)	8.5 (5, 3–9)

The trend analysis for age in the multivariable analysis yielded a *P* value of 0.11, with advanced age associated with a higher risk of adverse outcome. When the timing of treatment with neuraminidase inhibitors after the onset of influenza was analysed, the benefit was confined to administration within the first 48 h after the onset of symptoms.

Table 3 shows the variables associated with length of hospital stay. The use of neuraminidase inhibitors within the first 2 days after the onset of influenza reduced hospital stay by a mean of 1.9 days (from 6.6 to 4.7, $P<0.001$), whereas delayed administration was associated with an increase in hospital stay. Pneumonia diagnosed at admission was clearly associated with longer hospital stay, as were comorbidities (COPD, neurological impairment and cardiovascular disease) and some therapies (proton pump inhibitors).

Discussion

We found that traditional risk factors associated with hospitalization in patients with influenza (COPD and corticosteroid therapy before admission) were also found in our patients. Likewise, the use of neuraminidase inhibitors reduced the probability of adverse outcomes during hospital stay and significantly shortened the length of stay.

This study is observational and can be affected by several limitations. Kumar[11] has recently highlighted the drawbacks of observational studies in estimating the benefits of early viral treatment in the prognosis of flu. We agree that selection bias is difficult to avoid. Immortal time bias or survival-duration-related selection bias imply that the late use of antivirals may be related to a better prognosis, whereas in fact our results suggest the opposite.

Our results show no benefit of late neuraminidase treatment. In Israel, a retrospective cohort study documented a higher rate of complications after admission.[12] Severe complications (excluding hypoxia and uncomplicated pneumonia) occurred more frequently with late oseltamivir. In the same way, a Spanish study of ICU patients showed that ICU length of stay, days of mechanical ventilation and mortality were reduced in patients receiving early treatment versus late treatment with oseltamivir.[13] These reports do not give comparisons with flu patients without antiviral treatment.

The mortality rate in our study (1.2%) was low in comparison with other studies. This may be due to the fact that our patients were not all admitted to the ICU,[5,14] and did not all have pneumonia at hospital admission.[15] Even so, the mortality rate was clearly lower than that found in the USA at the beginning of the pandemic (7%)[4] or the 4.9% reported in Canada.[16]

Likewise, the rate of ICU admission (9.7%) was lower than that found in the USA (25%)[4] and Canada (16%),[16] although it was similar to the 8% reported in New Zealand Maoris.[17] Some form of selection bias cannot be completely ruled out as our study patients had to be interviewed to collect data on the use of medications before admission and other risk factors related to disease severity. In a study carried out in Catalonia (north-east Spain), of 773 cases hospitalized, 37.9% were admitted to the ICU.[18] In contrast, in Andalusia (southern Spain), 28 out of 311 hospitalized cases (9%) were admitted to an ICU.[19] In another Spanish study of patients admitted to the ICU, the mortality rate was 22%.[20] Taken together, these data suggest that patients who died shortly after admission were not picked up by our study.

The predisposing factors for a higher probability of adverse outcome during hospitalization were broadly similar to those found in other studies.[16,21] In one international series of patients with community-acquired pneumonia, male sex and obesity were predictors of mortality, although we did not find similar results.[15]

We found a significant association between reductions in ICU admission/death and the administration of neuraminidase inhibitors within the first 48 h after the onset of symptoms, similarly to the findings of Jain *et al.*[4] and other studies.[6,7] In these reports none of the pregnant women who died had taken neuraminidase inhibitors within the first two days after the onset of illness.

Early use of neuraminidase inhibitors was associated with shorter hospital stay. Other reports have found no relationship between antiviral treatment and hospital stay.[22]

In summary, we found that early treatment with neuraminidase inhibitors had a beneficial effect on outcomes during

Table 2. Association between study variables and ICU admission/in-hospital death, *n*

Variable	Total	*n* (%)	OR (95% CI)	OR[a] (95% CI)
Sex				
female	410	40 (9.8)	0.80 (0.50–1.28)	0.87 (0.54–1.40)
male	403	48 (11.9)	1 (ref.)	1 (ref.)
Age (years)				
≤18	195	13 (6.7)	1 (ref.)	1 (ref.)
19–45	275	27 (9.8)	1.52 (0.73–3.31)	1.33 (0.63–2.80)
46–65	242	33 (13.6)	2.21 (1.09–4.71)	1.56 (0.73–3.33)
≥66	101	15 (14.9)	2.44 (1.03–5.83)	1.86 (0.76–4.55)
Ethnicity				
Caucasian	708	82 (11.6)	0.46 (0.16–1.09)	0.56 (0.23–1.34)
other	105	6 (5.7)	1 (ref.)	1 (ref.)
Use of neuraminidase inhibitors				
yes	495	49 (9.9)	0.79 (0.49–1.26)	0.57 (0.34–0.94)
≤48 h within onset of symptoms	429	36 (8.4)	0.66 (0.39–1.09)	0.46 (0.27–0.80)
>48 h	66	13 (19.7)	1.75 (0.80–3.63)	1.29 (0.61–2.70)
no	318	39 (12.3)	1 (ref.)	1 (ref.)
Vaccinated with pandemic H1N1 vaccine				
yes	13	2 (15.4)	1.51 (0.16–7.08)	1.65 (0.33–8.23)
no	800	86 (10.8)	1 (ref.)	1 (ref.)
Vaccinated with seasonal influenza vaccine				
yes	155	15 (9.7)	0.86 (0.44–1.57)	0.60 (0.31–1.15)
no	658	73 (11.1)	1 (ref.)	1 (ref.)
Smoking				
ex-smoker	128	21 (16.4)	1.97 (1.07–3.52)	1.72 (0.94–3.13)
current	178	21 (11.8)	1.34 (0.74–2.37)	1.22 (0.68–2.18)
never	507	46 (9.1)	1 (ref.)	1 (ref.)
Alcoholism				
yes	44	8 (18.2)	1.91 (0.74–4.37)	1.46 (0.62–3.45)
no	769	80 (10.4)	1 (ref.)	1 (ref.)
COPD				
yes	76	14 (18.4)	2.02 (1.00–3.87)	1.76 (0.86–3.57)
no	663	74 (10.0)	1 (ref.)	1 (ref.)
Cardiovascular disease				
yes	70	13 (18.6)	2.03 (0.97–3.97)	1.56 (0.76–3.16)
no	7438	75 (10.1)	1 (ref.)	1 (ref.)
Diabetes				
yes	98	19 (19.4)	2.25 (1.21–4.02)	2.21 (1.21–4.02)
no	715	69 (9.7)	1 (ref.)	1 (ref.)
Liver failure				
yes	27	8 (22.9)	2.59 (0.98–6.09)	2.23 (0.93–5.34)
no	778	80 (10.3)	1 (ref.)	1 (ref.)
Corticosteroid therapy				
yes	31	8 (25.8)	3.05 (1.14–7.35)	3.37 (1.39–8.20)
no	782	80 (10.2)	1 (ref.)	1 (ref.)
Treatment with histamine-2 receptor antagonists				
yes	33	8 (24.2)	2.08 (1.05–6.66)	2.68 (1.14–6.36)
no	780	80 (10.3)	1 (ref.)	1 (ref.)

Continued

Table 2. *Continued*

Variable	Total	*n* (%)	OR (95% CI)	OR[a] (95% CI)
Pneumonia at admission				
yes	178	26 (12.8)	1.29 (0.76–2.14)	1.69 (0.98–2.93)
no	609	62 (10.2)	1 (ref.)	1 (ref.)
No. of comorbidities				
0	242	15 (6.2)	1 (ref.)	1[b] (ref.)
1	195	19 (9.7)	1.63 (0.76–3.56)	1.79 (0.88–3.65)
2–3	212	27 (12.7)	2.21 (1.09–4.60)	2.57 (1.31–5.03)
≥4	164	27 (16.5)	2.98 (1.47–6.24)	3.86 (1.91–7.79)

[a]Adjusted by age, sex, antiviral treatment before admission, pneumonia at admission, liver failure, diabetes, cardiovascular disease, treatment with histamine-2 receptor antagonists, corticosteroids, smoking and alcoholism.
[b]Adjusted by age, sex, antiviral treatment before admission and pneumonia at admission.

Table 3. Length of hospital stay (LOS) in days and association with study variables

	Crude LOS		Adjusted LOS	
Variable	mean (95% CI)	*P*	mean (95% CI)	*P*
Use of neuraminidase inhibitors				
yes				
≤48 h within onset of symptoms	4.9 (4.5–5.3)	0.001	4.7 (4.0–5.4)	<0.001
>48 h	9.4 (7.6–11.6)	0.001	8.8 (7.7–9.9)	0.014
no	6.3 (5.7–7.0)		6.6 (6.0–7.3)	
COPD				
yes	7.6 (6.2–9.2)	0.003	7.4 (5.9–9.1)	0.012
no	5.5 (5.2–5.9)		5.5 (5.2–5.9)	
Antibiotics before admission				
yes	6.1 (5.4–6.9)	0.196	6.2 (5.5–7.0)	0.073
no	5.5 (5.2–6.0)		5.5 (5.1–5.9)	
Corticosteroids before admission				
yes	5.6 (4.9–6.4)	0.861	5.8 (5.4–6.2)	0.056
no	5.7 (5.3–6.1)		5.1 (4.5–5.9)	
Proton pump inhibitors				
yes	7.4 (6.3–8.6)	0.001	6.6 (5.6–7.8)	0.032
no	5.4 (5.1–5.8)		5.5 (5.1–5.9)	
Pneumonia at admission				
yes	6.1 (5.4–6.9)	0.148	6.7 (5.9–7.6)	0.004
no	5.5 (5.2–5.9)		5.4 (5.0–5.8)	
Neurological impairment				
yes	7.8 (5.8–10.6)	0.034	8.5 (6.3–11.5)	0.006
no	5.6 (5.3–6.0)		5.6 (5.2–5.9)	
Ex-smoker				
yes	6.8 (5.8–7.8)	0.016	6.4 (5.5–7.4)	0.118
no	5.5 (5.1–5.9)		5.6 (5.2–5.9)	
Cardiovascular disease				
yes	8.5 (7.0–10.4)	0.001	7.6 (6.2–9.3)	0.005
no	5.5 (5.1–5.8)		5.5 (5.2–5.9)	

hospitalization and on the length of hospital stay in patients with HIN1 virus infection.

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Transparency declarations

None to declare.

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