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Antiviral treatment and vaccination for influenza A(H1N1)pdm09 virus: lessons learned from the pandemic

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A B S T R A C T

The influenza pandemic that was declared by the World Health Organization in June 2009 created a new scenario for the use of influenza antivirals and vaccination. The new strain, influenza A(H1N1)pdm09, was resistant to amantadine and rimantadine, and the most frequently used antiviral was oseltamivir. Randomized studies were not performed comparing neuraminidase inhibitors with placebo. Nevertheless, experience from prospective and retrospective cohorts indicated that these drugs were useful for improving the prognosis of patients admitted to hospitals, especially for those with more severe disease. Treatment with oseltamivir was associated with a reduction in days of fever, length of hospital stay, use of mechanical ventilation and mortality. Treatment was more effective if it was begun within the first 48 h after the onset of symptoms, but it was also useful if begun later. A safe and effective vaccine to prevent disease from this new influenza strain was available in developed countries soon after the pandemic began; thus, the rate of adverse effects was comparable to that of seasonal influenza vaccines. The main barrier to its use was the concern of target populations about its necessity and safety. Therefore, the challenges for future pandemics will be to increase the population coverage of the vaccine in developed countries and to make it affordable for developing countries.

Tratamiento antiviral y vacunación para el virus de la gripe A(H1N1)pdm09: lecciones aprendidas de la pandemia

Palabras clave:
Virus de la gripe A (H1N1)pdm09
Oseltamivir
Inhibidores de la neuraminidasa
Vacuna

R E S U M E N

La pandemia de gripe declarada por la Organización Mundial de la Salud en junio de 2009 abrió un nuevo escenario para el empleo de antivirales y vacunas activos frente a este virus. La nueva cepa de virus de la gripe de tipo A(H1N1)pdm09 era resistente a amantadina y rimantadina. El antiviral más empleado fue oseltamivir. No se desarrollaron estudios aleatorizados de antivirales frente a placebo. No obstante, la experiencia acumulada mediante el estudio de cohortes prospectivas y retrospectivas indica que estos fármacos fueron útiles para mejorar el pronóstico de los pacientes ingresados en el hospital, especialmente de aquellos con formas más graves de la enfermedad. El tratamiento con oseltamivir se asoció a una disminución de los días de fiebre, de la duración de la estancia hospitalaria, de la necesidad de ventilación mecánica y de la mortalidad. El tratamiento fue más efectivo cuando se inició en las primeras 48 h desde el inicio de los síntomas pero fue útil incluso cuando se inició más tarde. La vacuna activa frente a esta nueva cepa estuvo disponible en los países desarrollados poco tiempo después de la declaración de la pandemia, demostrando eficacia y seguridad. La tasa de efectos adversos fue comparable a la de las vacunas de la gripe estacional. El mayor obstáculo para su empleo fueron las dudas sobre su eficacia y seguridad por parte de las poblaciones susceptibles de ser vacunadas. Por tanto, el reto para futuras pandemias será aumentar la cobertura vacunal en los países desarrollados y conseguir que la vacuna esté disponible para los países en vías de desarrollo.

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Introduction

In April 2009, a novel influenza virus, now referred to as the influenza A(H1N1)pdm09 virus, caused an outbreak of respiratory disease in Mexico[1] and spread rapidly worldwide.[2] Spain was the first country in Europe to report a laboratory-confirmed case of infection by the influenza A(H1N1)pdm09 virus.[3] This first influenza pandemic of the twenty-first century was an ideal opportunity to study the usefulness of antivirals and vaccination for the treatment and prevention of this disease. As the development of a vaccine for the new strain of influenza virus took some time, antivirals were the cornerstone of the initial approach to the pandemic influenza in 2009.

The purpose of this article is to summarize the experience of the Spanish Network for Research in Infectious Diseases (REIPI) with regard to influenza A(H1N1)pdm09 antiviral treatment and prophylaxis. We also performed a literature review on these issues.

What did we know about antiviral treatment for influenza before the 2009 pandemic?

Four drugs have been developed for the prophylaxis or treatment of the influenza virus infection: the adamantanes (amantadine and rimantadine) and the neuraminidase inhibitors (zanamivir and oseltamivir). The adamantanes block the M2 protein of the virus coat and are associated with several toxic effects and with the rapid emergence of drug-resistant variants. The influenza A(H1N1)pdm09 was resistant to these types of drugs, which made them useless during the 2009 pandemic.[4]

Neuraminidase is a protein present in the coating of the influenza virus. Its action is key for the release of progeny viruses from infected host cells. Neuraminidase inhibitors block the action of this protein, thus preventing the infection of new host cells and interrupting the spread of the infection in the respiratory tract.[5] Replication of the influenza virus in the respiratory tract reaches its peak between 24 and 72 h after the onset of illness, thus neuraminidase inhibitors that act at this point of replication should be administered as early as possible after the illness begins. Zanamivir is administered by oral inhalation and oseltamivir is administered orally.

Before the 2009 influenza pandemic, neuraminidase inhibitors had been used both for the prophylaxis and treatment of influenza.[5] A meta-analysis published in 2009.[6] analyzed published reports of randomized studies performed on healthy adults and concluded that neuraminidase inhibitors were useful in the prevention of microbiologically confirmed influenza: risk ratio (RR) 0.41 (95% confidence interval [95% CI], 0.25-0.65). The analysis also demonstrated that neuraminidase inhibitors have an effect (compared with placebo) on the alleviation of influenza symptoms: hazard ratio=1.22 (95%CI, 1.14-1.31). This study also analyzed the effect of oseltamivir on the prevention of complications requiring treatment with antibiotics (pneumonia, bronchitis or "other lower respiratory tract infections"). In this case, the meta-analysis did not show any difference between oseltamivir and placebo: RR: 0.55 (95%CI, 0.22-1.35).

A recent study.[7] by the same authors raises concern about the quality of the information available for neuraminidase inhibitors, given that 60% of the patient data from phase III oseltamivir treatment trials have never been published. Other reviewers highlight the necessity of more evidence to guide decision-making about when and for whom to use antivirals for influenza.[8]

What was the experience with neuraminidase inhibitors during the 2009 influenza pandemic?

To the best of our knowledge, no prospective comparative clinical trial was developed during the 2009 influenza pandemic regarding neuraminidase inhibitors. The information available regarding their usefulness is derived from observational retrospective or prospective cohorts. It would likely have been considered unethical to perform randomized trials against placebo or delay treatment in the context of a pandemic.

The Novel Influenza A (H1N1) Study Group of the Spanish Network for Research in Infectious Diseases (REIPI) performed an observational analysis of a prospective cohort of adults hospitalized for influenza A(H1N1)pdm09 at 13 Spanish hospitals from June 2009 to November 2009. The total number of subjects included in this cohort was 585, with a median age of 39 years (range 16-87). A 54% presented with at least 1 comorbid condition, and 16.8% were pregnant women. The median time from onset of symptoms to hospitalization was 3 days (range 0-21). Regarding treatment, 93% of patients were treated with antivirals and 71% received antibiotics. Twelve percent were admitted to the intensive care unit (ICU), and in-hospital mortality was 2.2%.[9]

The relationship of precocity in the administration of oseltamivir to prognosis was assessed.[10] The median time from onset of symptoms to oseltamivir administration was 3 days (interquartile range 2-5 days). After adjustment for confounding factors, the time from onset of symptoms to oseltamivir administration (+1 day increase) was associated with a prolonged duration of fever (odds ratio [OR]: 1.10; 95%CI, 1.02-1.19), a prolonged length of stay (LOS) (OR: 1.07; 95%CI, 1.00-1.15) and an increased mortality rate (OR: 1.20; 95%CI, 1.06-1.35) (Tables 1 and 2). As there were no homogeneous criteria for admission, the subgroup of patients with progressive, severe or complicated illness at hospital admission was specifically analyzed. This subgroup was defined by any of the following categories: *a)* signs or symptoms of lower respiratory tract infection (including pneumonia); *b)* altered mental status; *c)* hypotension, and *d)* bacterial

Table 1
Outcomes stratified by groups of time from onset of symptoms to oseltamivir administration in hospitalized patients with influenza A(H1N1)pdm09 virus disease (univariate analysis)

Time from onset of symptoms to antiviral administration	Median duration of fever (days-IQR)	Fever above the median (2 days) %[a]	Median LOS (days-IQR)	LOS above the median (5 days) %[b]	Use of mechanical ventilation %[c]	Mortality %[d]
≤2 days	1 (1-2)	20.2	5 (3-7)	41.7	6.9	0
3-4 days	2 (1-3)	33.1	5 (3-7)	40.5	7.5	1.9
5-6 days	2 (1-3)	37.5	6 (4-8)	54.7	8	3.4
≥7 days	2 (1-4)	42	7 (5-12)	68.2	18	5.6

IQR: interquartile range; LOS; length of stay.
[a]Chi square test for trend P=.001.
[b]Chi square test for trend P≤.001.
[c]Chi square test for trend P=.008.
[d]Chi square test for trend P≤.001.
Adapted from Viasus et al.[10]

Table 2
Multivariate analysis of factors associated with mortality in hospitalized patients with influenza A(H1N1)pdm09 virus infection

Variables	OR	95%CI	*P*
Age (<50 years)	3.36	0.66-17.1	.13
Comorbidities	9.80	1.22-78.6	.03
Time from onset of symptoms to oseltamivir administration	1.20	1.06-1.35	.004

95% CI: 95% confidence interval; OR: odds ratio.
Adapted from Viasus et al.[10]

co-infection based on laboratory testing. A multivariate logistic regression analysis was performed. Also in this subgroup, the time from onset of symptoms to oseltamivir administration (+1 day increase) was independently associated with a prolonged duration of fever (OR: 1.11; 95%CI, 1.01-1.20), a prolonged LOS (OR: 1.10; 95%CI, 1.01-1.20) and higher mortality (OR: 1.19; 95%CI, 1.05-1.36). As the median time from onset of symptoms to oseltamivir administration was 3 days, an important finding of this study is that patients appeared to benefit from oseltamivir therapy even when it was initiated more than 48 h after the initial symptoms.

In this same study,[10] there was concern about the possibility that these results depended on the time from onset of symptoms to hospital admission. An analysis considering the time from admission to initiation of treatment with oseltamivir was performed (Table 3). Among the 538 admitted patients treated with oseltamivir, 411 initiated treatment within the first 24 h after admission and 127 began treatment more than 24 h after admission. The delay in oseltamivir administration (>24 h) was independently associated with prolonged duration of fever (adjusted OR: 1.67; 95%CI, 1.03-2.62), prolonged LOS (adjusted OR: 1.67; 95%CI, 1.06-2.63), use of mechanical ventilation (adjusted OR: 3.13; 95%CI, 1.56-6.27) and increased mortality (adjusted OR: 4.29; 95%CI, 1.25-14.63).

This cohort was also analyzed to compare those hospitalized subjects with or without pneumonia.[11] Among the 234 (43.1%) patients with pneumonia, 174 (82.8%) had primary viral pneumonia and 36 (17.2%) had secondary bacterial pneumonia. The prognosis of those who developed pneumonia was poorer. Compared with patients without pneumonia, those with pneumonia more frequently had shock (9.8% vs. 1%; *P*<.001), required ICU admission (22.6% vs. 5.8%; *P*<.001), underwent mechanical ventilation (17.9% vs. 3.2%; *P*<.001) and had a longer LOS (median 7 days vs. 5 days; *P*<.001). Moreover, in-hospital mortality was significantly higher in those who developed pneumonia (5.2% vs. 0%; *P*<.001). In this study, the prevalence of pneumonia was significantly related to the time from onset of symptoms to antiviral administration (≤2 days: 20.4%; 3-5 days: 32.7%; ≥6 days: 60.7%; *P*<.001, chi-squared for trend). Early oseltamivir administration, which was when the first dose was administered to patients in less than 48 h after the onset of symptoms, was provided to only 22.4% of patients who developed pneumonia compared with 49.3% of those who did not (*P*<.001). A multivariate analysis of the risk factors for developing pneumonia was performed. Early administration of oseltamivir was a protective factor (OR: 0.29; 95%CI, 0.19-0.46). As previously stated, the main limitation of this study was that hospital admission criteria were not standardized.

This Spanish cohort was also analyzed to define risk factors for severe disease.[9] Severe disease was defined as the composite outcome of ICU admission or in-hospital mortality. Severe disease occurred in 75 (12.8%) of the 585 hospital-admitted patients. Seventy-one required ICU admission and 13 died. Once again, early oseltamivir therapy was a protective factor against this composite outcome of severe disease (OR: 0.32; 95%CI, 0.16-0.63).

Other studies developed during the 2009 pandemic demonstrated a positive relationship between treatment with neuraminidase inhibitors and the prognosis of influenza infection.[12,13] A retrospective cohort of 1291 Chinese patients demonstrated that treatment with oseltamivir significantly protected against the development of pneumonia (OR: 0.12; 95%CI, 0.08-0.18), and that treatment started within 2 days of the onset of symptoms reduced the duration of fever and viral RNA shedding.[14] Other studies have demonstrated a reduction in viral shedding when treatment with oseltamivir was initiated within the first 3 days of illness.[15,16] Among 58 patients admitted to the ICU in Mexico, neuraminidase inhibitor treatment (vs. no treatment) was associated with improved survival (OR: 8.5; 95%CI, 1.2-68.8).[17] Oseltamivir also demonstrated its usefulness in such special populations as critically ill children,[18] pregnant women,[19-21] solid organ transplant recipients[22] and HIV-infected subjects.[23,24]

During the 2009 pandemic, oseltamivir was used for prophylaxis in some settings. A study was developed in Singapore of 1175 military personnel in a semi-closed environment, of which oseltamivir was given as prophylaxis to 1100. A total of 75 people (6.4%) were infected before the intervention compared with 7 (0.6%) after the intervention. No severe adverse effects were reported.

Influenza A(H1N1)pdm09 resistance to oseltamivir was described a few months after the beginning of the pandemic,[25,26] and clinical situations in which testing for antiviral-resistance would be indicated have been highlighted.[25] Intravenous zanamivir[27] was used as an alternative to oseltamivir for the treatment of patients with infection by oseltamivir-resistant strains. The new intravenous neuraminidase inhibitor peramivir was also used as an alternative to oseltamivir during the pandemic.[28]. Nevertheless, the available data was insufficient to assess whether peramivir affected outcome or caused serious adverse effects.[28]

Apart from antivirals, other therapeutic approaches were used during the pandemic. Concomitant treatment with steroids (37 patients), macrolides (31 patients) or statins (12 patients) did not prevent the development of severe disease among patients with influenza pneumonia included in the observational cohort of the Novel Influenza A (H1N1) Study Group of the REIPI.[29] Other non-comparative studies could not demonstrate a definitive benefit of steroids as a concomitant treatment for patients with severe forms of influenza.[30-32] Extracorporeal membrane oxygenation was also

Table 3
Effect on outcomes of delay of oseltamivir administration after arrival at the hospital in hospitalized patients with influenza A(H1N1)pdm09 virus infection

	Oseltamivir administration after arrival at the hospital				
Outcomes (%)	≤24 h	>24 h	*P*	Crude OR (95%CI)	Adjusted OR (95%CI)
Fever above the median (2 days)	27.9	38.4	0.04	1.61 (1.01-2.57)	1.67 (1.03-2.72)
LOS above the median (5 days)	44	60.3	0.001	1.93 (1.29-2.91)	1.67 (1.06-2.63)
Use of mechanical ventilation	6.1	18.9	< 0.001	3.59 (1.97-6.56)	3.13 (1.56-6.27)
Mortality	1.2	4.7	0.02	4.02 (1.20-13.4)	4.29 (1.25-14.6)

95%CI: 95% confidence interval; LOS: length of stay; OR: odds ratio.
Adapted from Viasus et al.[10]

used in 2009 for the treatment of severe influenza-related acute respiratory distress syndrome.[33,34] although its indication in this context remains uncertain.[35]

How has the experience gained from the use of neuraminidase inhibitors during the pandemic been applied in more recent influenza seasons?

Influenza A(H1N1)pdm09 is expected to circulate as a seasonal virus for some years after the pandemic. The Spanish group analyzed a prospective cohort study of hospitalized adults with influenza A(H1N1)pdm09 pneumonia at 14 teaching hospitals to compare the epidemiology, clinical features and outcomes of influenza A(H1N1) pdm09 pneumonia between the pandemic period and the first post-pandemic influenza season (2010-2011).[36] A total of 348 patients were included, 234 of whom were admitted during the pandemic period and 114 during the first post-pandemic season. Patients in the post-pandemic season were significantly older and had more chronic underlying diseases. Unfortunately, the time from onset of illness to the administration of antiviral therapy was longer in the second period (P<.002), and early antiviral therapy (≤48 h) was less frequently administered (22.9% vs. 10.9%; P=.009). These data were associated with a higher rate of ICU admission, a higher rate of mechanical ventilation and higher in-hospital mortality (5.1% vs. 21.2%; P<.001). This delay in the initiation of antiviral treatment occurred despite the World Health Organization's strong recommendation for the early administration of antiviral treatment to all patients hospitalized for influenza during the post-pandemic period.[37]

What was the experience with vaccination during the 2009 influenza pandemic?

Vaccination has been traditionally considered the primary strategy for the prevention of influenza and the most effective way to mitigate the negative effects of a pandemic.[38] The World Health Organization officially declared the beginning of the first influenza pandemic (phase 6 status) of the 21st century on June 11th, 2009. A vaccine for influenza A(H1N1)pdm09 was available in many countries from September 2009.

Many prospective and randomized studies were developed to assess the immunogenicity and safety of the vaccine during the 2009 pandemic.[39-41] A systematic review and meta-analysis of the immunogenicity and safety of the influenza A(H1N1)pdm09 vaccine has been performed.[42] that included 16 studies covering 17,921 subjects. Adequate seroprotection (≥70%) was achieved in almost all age groups, even after a single dose and at low antigen content (except in children under 3 years of age, who received one dose of the non-adjuvanted vaccine). Non-adjuvanted vaccines from international companies and adjuvanted vaccines containing an oil in water emulsion obtained very good rates of seroprotection. The use of aluminum derivatives as adjuvants did not improve the immune response when compared with non-adjuvanted vaccines.[42] Only 2 severe adverse events and no deaths related to vaccination were reported among these subjects. There was great concern about a possible relationship between the influenza pandemic vaccine and Guillain-Barré syndrome because of a relationship that had been found between this neurologic disease and the 1976 H1N1 influenza vaccine. A recent report of the results of a population-based survey involving more than 45 million people found a rate of 0.74 more cases of Guillain-Barré syndrome per million doses of influenza A(H1N1)pdm09 vaccine (95%CI, 1.02-2.21).[43] This excess risk is comparable to some previous seasonal influenza vaccine risk assessments.[43]

The effectiveness and safety of the influenza A(H1N1)pdm09 vaccine has also been evaluated in immune-suppressed patients, as observed in those receiving a solid organ transplantation (SOTR).[44] In a multicenter prospective study carried out on 346 patients from 3 Spanish hospitals participating in the REIPI network, the immunogenicity, efficacy and safety of the pandemic vaccine in SOTR were evaluated. Rates of seroconversion and seroprotection after vaccination were 73.1% and 82.9%, respectively. Patients with baseline antibody titers had better geometric mean titers after the pandemic vaccination. Younger age, liver disease and m-TOR inhibitor therapy were independently associated with lower seroprotection; there were no major adverse effects or rejection episodes. Thus, the pandemic vaccine was safe in SOTR and elicited an adequate response.

During the second wave of the pandemic (September-December 2009), Public Health authorities attempted to mitigate the effects of the infection by promoting mass vaccination campaigns. The target population for vaccination varied from country to country, but vaccination met with limited success for a variety of reasons. In Spain, coverage was generally low, with reported rates of only 14.6% and 16.5% among individuals with chronic conditions and hospital workers, respectively.[45,46] To develop successful vaccination programs for future pandemics, it is important to understand the factors that influenced vaccination during the 2009 pandemic.[47-48] Various studies.[47-48] found the following as factors positively associated with vaccination: male sex, younger age, higher education, being a doctor, being in a priority group for which vaccination was recommended, receiving a prior seasonal influenza vaccination, believing the vaccine to be safe and/or effective and obtaining information from official medical sources. Some authors have suggested that clinicians should act as "armchair epidemiologists" to convince subjects belonging to groups at high risk for developing complications during an influenza infection of the importance of being vaccinated.[49]

The main challenge for the next pandemic in regard to vaccination will be to convince the population in developed countries of the safety and effectiveness of the vaccine.[50] and to make the vaccine affordable for developing countries.[51] Continued efforts should be made to develop a universal vaccine that is active against conserved antigens common to every type of influenza virus and produced in a non-egg-based culture system.[52]

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Conflicts of interest

All authors declare that they have no conflicts of interest in this article.

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