

Clinical Experience in Adults and Children Treated with Intravenous Peramivir for 2009 Influenza A (H1N1) Under an Emergency IND Program in the United States

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(See the editorial commentary by Jain et al, on pages 707–709.)

Background. Peramivir, an investigational intravenous neuraminidase inhibitor in Phase 3 trials for hospitalized patients, was made available during the 2009 H1N1 influenza pandemic under the Emergency Investigational New Drug (eIND) regulations. We describe the clinical characteristics and outcomes of all patients for whom peramivir was requested under the eIND.

Methods. After obtaining eIND approval from the Food and Drug Administration and local institutional review board approval, clinicians caring for hospitalized patients with influenza administered intravenous peramivir and collected information on demographic characteristics, clinical characteristics, and outcomes.

Results. From April through October 2009, peramivir was requested for 42 patients and administered to 20 adults and 11 children. At hospitalization, all patients had rapidly progressing, radiographically confirmed viral pneumonia with respiratory failure, and all but 1 patient required mechanical ventilation. In most patients, including 1 person with documented oseltamivir-resistant infection, the illness had progressed despite oseltamivir treatment. Peramivir was administered for 1–14 days (median duration, 10 days). The 14-day, 28-day, and 56-day survival rates were 76.7%, 66.7%, and 59.0%, respectively. Peramivir was generally well tolerated.

Conclusions. Intravenous peramivir was well tolerated and was associated with recovery in most patients hospitalized with severe 2009 H1N1 influenza viral pneumonia and treated under an eIND.

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On 26 April 2009, the US Secretary of Health and Human Services declared a public health emergency due to the 2009 influenza A H1N1 virus (2009 H1N1) infection pandemic [1]. Compared with seasonal influenza, the number of hospitalizations, admission to intensive care units, and invasive life support were disproportionately high among children and young adults [2–4], whereas underlying medical conditions, especially immunosuppression, obesity, and pregnancy, were identified as risk factors for hospitalization [2, 3, 5, 6]. In the face of this

emergency and the lack of Food and Drug Administration (FDA)-approved intravenous (IV) neuraminidase inhibitors (NAIs) to treat seriously ill hospitalized patients, the FDA acted to make peramivir, an investigational IV NAI, available.

Use of NAIs in previously healthy outpatients with uncomplicated seasonal influenza is associated with a reduction in the duration of viral shedding and in the duration of clinical signs and symptoms [7, 8]. Retrospective studies involving hospitalized patients with influenza have reported a reduction in viral replication, improved survival, and possibly shorter duration of hospitalization when NAIs are used early in the course of illness [9, 10]. Based on these data and on early data among hospitalized patients infected with 2009 H1N1 [3, 4], the Centers for Disease Control and Prevention and the World Health Organization recommended early institution of antivirals for all hospitalized persons with suspected or confirmed influenza [11, 12].

Peramivir, like the FDA-approved NAIs oseltamivir (oral) and zanamivir (inhaled), inhibits the viral neuraminidase enzyme and is active against influenza A and B virus, including the novel 2009 H1N1 virus in *in vitro* assays and animal models [13–16]. Over 2300 subjects, either healthy or with influenza infection, have received peramivir in clinical trials, where it has been generally well tolerated. Receipt of peramivir reduced time to alleviation of symptoms, compared

with placebo [17], and demonstrated clinical efficacy and tolerability similar to that of oral oseltamivir in outpatients [18] and in hospitalized adults with seasonal influenza [19]. Peramivir is currently undergoing US Phase 3 trials involving hospitalized patients with influenza and was recently approved in Japan and South Korea.

To make peramivir available by Emergency Use Authorization (EUA), the FDA initiated a series of site visits and audits, review of data, and preparation of documentation for clinicians. While these steps occurred (April–October 2009), the FDA requested that BioCryst Pharmaceuticals provide peramivir under FDA Emergency Investigational New Drug (eIND) regulations (21 CFR 312.56) to treat individual severely ill hospitalized patients upon request from any licensed clinician in the United States. The EUA was initiated on 23 October 2009 [20], effectively ending the eIND.

This report is a retrospective review of all patients for whom eIND requests for peramivir were received by BioCryst for the treatment of confirmed or suspected 2009 influenza A(H1N1) from April through 23 October 2009.

METHODS

Under the conditions of the eIND process, clinicians requested peramivir if they believed that such use was in the best

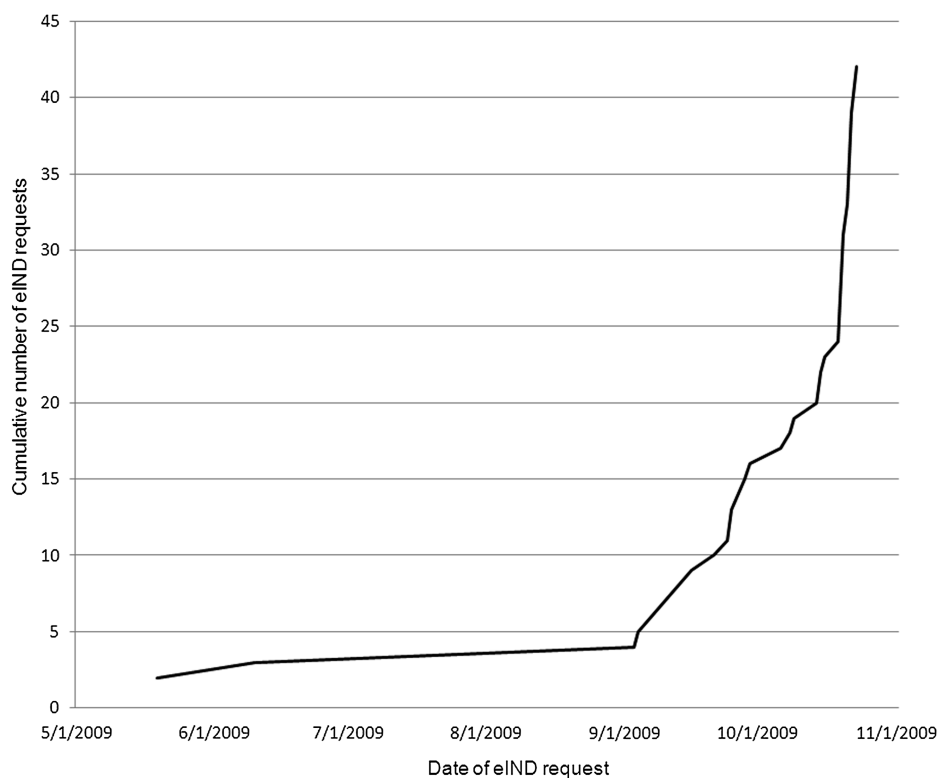


Figure 1. Cumulative requests received for peramivir from April through 23 October 2009 under the Emergency Investigational New Drug (eIND) regulations.

interest of their patient; no severity requirement was imposed by the FDA or BioCryst nor were subjects required to have experienced the failure of other drug regimens. The availability of this investigational IV NAI was made public through the BioCryst web site, through the media, and by personal communication.

Upon notification of FDA eIND approval from the clinician, BioCryst provided the drug, investigator brochure, drug dosing and preparation instructions, and a sample informed consent form. The clinician obtained institutional review board approval and informed consent and submitted the required documentation to the FDA within 5 days of drug initiation.

Peramivir was supplied in 200 mg/20 mL single-use vials to be diluted in sodium chloride injection, United States Pharmacopeia. The adult recommended dosage was 600 mg IV once daily, with adjustments for renal impairment. Because no pediatric patients had received peramivir, the recommended pediatric dosage was based upon pharmacokinetic modeling, ranging from 6 mg/kg to 12 mg/kg, not to exceed 600 mg IV per day [14]. Within 2 weeks of the patient's last peramivir dose, all unused drug was to be destroyed.

Data were collected using a standardized case report form to assess demographic characteristics, underlying conditions, illness onset and severity, laboratory results, treatment, and outcomes. Severity of illness was assessed using a modified Acute Physiology and Chronic Health Evaluation (APACHE) II score calculated from data submitted with the request. In the event of a serious adverse event or death, a MedWatch form was to be submitted to the FDA and a copy sent to BioCryst. Data were collected for patients for at least 56 days after peramivir treatment was initiated. Follow-up status as of February 2010 was determined by case report form data; missing data were clarified via direct email or telephone contact with the patient's clinician. Upon request from clinicians, blood samples were shipped to BioCryst for therapeutic drug monitoring (TDM), as previously described [21].

Demographic and clinical characteristics were summarized using descriptive statistics. Univariate logistical regression was performed to assess the potential risk factors predictive of mortality. Odds ratios and 95% confidence intervals (CIs) were calculated for each factor. Survival at 14, 28, and 56 days was estimated based on the method of Kaplan-Meier.

RESULTS

eIND Requests

Requests for peramivir were received for 42 patients from 18 states from April 2009 through 23 October 2009. Three requests were received in May and June, and the remaining 39 requests were received from September through October, correlating with the second wave of pandemic influenza in the

Table 1. Demographic Characteristics and Co-morbidities on Day of eIND Request

Parameter	Peramivir-treated patients (n = 31)
Age group^a	
0–4	1 (3)
5–9	2 (6)
10–17	8 (26)
18–49	14 (45)
50–64	5 (16)
≥65	1 (3)
Sex	
Male	18 (58)
Female	13 (42)
Race	
Caucasian	28 (90)
Other	3 (10)
Ethnicity	
Non-Hispanic	23 (74)
Hispanic	7 (23)
Unspecified	1 (3)
BMI, median value (range)	28 (12.5–50.0)
Prior medical condition	
Obesity (BMI ≥ 30)	11/31 (35)
Severe obesity (BMI ≥ 40)	3/31 (10)
COPD/asthma	7/31 (23)
Pregnant or post-partum	3/13 (23)
Cancer	2/31 (6)
Diabetes	3/31 (10)
Solid-organ transplantation	2/31 (6)
Hematopoietic stem cell transplantation	1/31 (3)
Corticosteroid use	5/31 (16)
Influenza severity	
Pneumonia with respiratory failure	31/31 (100)
Mechanical ventilation required	30/31 (97)
Vasopressor support required	17/31 (55)
APACHE II score ≥ 20	19/31 (61)
Acute renal failure	13/31 (42)
Dialysis required	11/31 (35)
Acute heart failure	6/31 (19)
Liver failure	4/31 (13)
APACHE II score, median value (range)	22 (5–37)
Other neuraminidase treatment	
Oseltamivir	27/31 (87)
Zanamivir	1/31 (3)
None	3/31 (10)
Unknown	1/31 (3)

NOTE. Data are no. (%) or proportion (%) of patients, unless otherwise indicated. APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index, calculated as the weight in kilograms divided by the square of height in meters; COPD, chronic obstructive pulmonary disease.

^a The median age of the patients was 23.0 years (range, 3 months to 76 years).

Table 2. Characteristics of Pediatric and Pregnant or Post-partum Patients Treated with Peramivir

Age	Sex	Presentation	Prior TX	Peramivir TX	Clinical course	Outcome	Comments
Pediatric patients							
15	M	Fever, pneumonia, CHF, respiratory failure, myocarditis.	O, A	HD6–16 600 mg/d	HD1: intubation, ECMO, mechanical ventilation. Pulmonary improvement with peramivir. Multiple medical complications. Vasopressor support due to heart failure.	Transferred from PICU to another hospital on HD110	Awaiting heart transplant
17	M	3-d HX URI. Pneumonia.	O	HD3–8 600 mg/d	Respiratory failure, intubation, mechanical ventilation, worsening to require HFO. Vasopressor support. Renal failure. Pulmonary improvement with peramivir. Extubation HD19. Cardiac and hepatic dysfunction persisted. Discharged HD27.	Recovered	Rehab required
15	F	Pneumonia.	O, A, R	HD6–7 600 mg/d	HD3: Intubation, mechanical ventilation, HFO. Vasopressor support. Initial improvement on peramivir. Worsening HD7 required transfer to hospital with ECMO. Peramivir discontinued.	Recovered	On HD25, patient improved and off ventilator support. Eventually discharged home.
10	M	5-d HX URI. Pneumonia, leucopenia, respiratory failure, renal failure.	O	HD8–22 2.2 mg/kg adjusted to 5.4 mg/kg with TDM	ARDS, intubation. Progressive respiratory failure. ECMO initiated on HD7. Renal failure required CVVH. Immunosuppressive drugs discontinued. Hypotension requiring inotropic support. Viral shedding continued through HD14; absent HD37. Extubated HD43. Discharged HD72.	Recovered	HX renal transplant. H275Y mutation, O resistance
11	F	5-d HX fevers, HA, URI, vomiting, diarrhea. Pneumonia, acrocyanosis.	O	HD2–12 10 mg/kg	Respiratory failure, intubation, mechanical ventilation. Clinical status improved. Extubated HD6. Radiographs HD7 showed complete resolution. Discharged HD12 in stable condition.	Recovered	Peramivir PK on HD3 shown in Figure 2 and chest radiographs on HD1 and HD9 in Suppl. Appendix.

Table 2. (Continued)

Age	Sex	Presentation	Prior TX	Peramivir TX	Clinical course	Outcome	Comments
13	M	Influenza.	O	HD16–25 600 mg/d	Respiratory failure, intubation, mechanical ventilation, ECMO. Vasopressor support. Improvement in respiratory and hemodynamic parameters after peramivir. HD30: remained critically ill on ECMO.	Died HD53 ^a	HX of asthma
5	M	14-d HX URI.	O	HD16–26 10 mg/kg	Respiratory failure, intubation, mechanical ventilation HD5 and eventually ECMO. Clinically comatose, heart failure.	Died HD34 ^a	Medical support withdrawn per family request.
0.3	F	2-d HX influenza.	O	HD2–12 2.2 mg/kg adjusted by TDM	HD1: hypotension, unresponsiveness requiring intubation, myocarditis, intracranial hemorrhage, acute renal failure requiring CVVH, ECMO. Cardiac contractility improved dramatically with peramivir. ECMO continued 6 days. Renal failure reversing by HD6. Line-related <i>Candida</i> infection and CA-MRSA treated. Discharged HD57.	Recovered	
14	F	4-d HX URI. Pneumonia and respiratory failure.	O	HD14–20 10 mg/kg	Respiratory failure, intubation, mechanical ventilation. Deteriorated, requiring HFO and vasopressor support.	Died HD20 ^a	HX of asthma and chronic renal failure
13	M	HX URI.		HD2–10 10 mg/kg	HD1: pneumonia, respiratory failure, intubation, mechanical ventilation. Vasopressor support. Respiratory status improved on peramivir. Discharged home HD14.	Recovered	
8	M	4-d HX otitis media. Respiratory distress, cyanosis and impending respiratory failure.	O	HD10–18 10 mg/kg	Cardiac arrest HD1 with resuscitation, intubation. Radiographs with severe atelectasis. Intubated, mechanically ventilated. Worsening oxygenation led to ECMO on HD3. Lung function improved by HD14, allowing decannulation and HFO. MRI HD31 revealed diffuse cerebral ischemia and atrophy, likely sequelae of cardiopulmonary arrest.	Died HD35 ^a	HX Noonan syndrome, congenital heart disease and defects, congenital pulmonary hypertension, spinal fusion for scoliosis. Medical support withdrawn per family request. Chest radiographs HD10 and HD19 in Supplemental Appendix.

Table 2. (Continued)

Age	Sex	Presentation	Prior TX	Peramivir TX	Clinical course	Outcome	Comments
Pregnant/post-partum patients							
28	F	3-d HX symptoms. Pneumonia.	O	HD6–15	Respiratory failure, intubation, mechanical ventilation. Emergency C-section delivered healthy baby HD2. Respiratory deterioration requiring high FiO ₂ , PEEP. Clinical status improved gradually. Tracheostomy with insertion of PEG tube. Transferred to LT care HD23. Continued improvement, extubation.	Recovered	Peramivir PK on HD8 shown in Figure 3.
22	F	7-d HX symptoms. Pneumonia.	O	HD4–8	Respiratory failure, intubation, mechanical ventilation, AC. Vasopressor support. Discharged HD12.	Recovered	HX of asthma. Subsequently delivered healthy baby.
23	F	4-d HX ILI. Pneumonia and respiratory failure.	O	HD2–12	Respiratory failure, intubation, mechanical ventilation. Oseltamivir treatment initiated HD1 for 3 days. Recovered slowly; extubated after 27 days. Discharged HD38.	Recovered	HX of asthma. Twenty-two weeks pregnant. Subsequently delivered healthy baby.

NOTE. A, amantadine; AC, assist control; ARDS, acute respiratory distress syndrome; CHF, congestive heart failure; CVVH, continuous venovenous hemofiltration; ECMO, extracorporeal membrane oxygenation; FiO₂, fraction of inspired oxygen; HA, headache; HD, hospital day; HFO, high-frequency oscillation; HX, history; ILI, influenza-like illness; LT, long term; O, oseltamivir; PEEP, positive end expiratory pressure; PEG, percutaneous endoscopic gastrostomy; PICU, pediatric intensive care unit; R, ribavirin; TDM, therapeutic drug monitoring; TX, treatment; URI, upper respiratory infection.

^a See primary cause of death in Table 3; PK, pharmacokinetic.

United States (Figure 1). Two requests were withdrawn. Median time from eIND request to drug receipt was 21 h (range, 3–50 h); the time required for shipping drug supply from a central repository was the major contributor (range, <1 to 48 h) to this delay. In 9 cases, the drug was not administered because death ($n = 5$) or recovery ($n = 4$) ensued prior to drug administration. Peramivir was administered to the remaining 31 patients; all subsequent results reflect data collected from only those treated patients.

Clinical and Virologic Findings

Peramivir-treated patients were mostly children and young adults (Table 1; Supplementary Appendix Tables S1–S2). Eleven patients (35%) were <18 years of age, and 3 of 13 women were pregnant ($n = 2$) or immediately post-partum ($n = 1$). All patients were admitted to an intensive care unit with fever and rapidly progressing radiologically confirmed pneumonia. Most patients (55%) were without known underlying medical conditions prior to influenza onset; 11 patients (35%) were obese (defined as a body mass index ≥ 30 , calculated as the weight in kilograms divided by the square of

height in meters). Six of these 11 patients had no other underlying conditions. Common underlying conditions were asthma or chronic obstructive pulmonary disease (23%) and compromised immunity (23%). Laboratory findings are summarized in Supplementary Appendix Tables S3–S4. Patients with eIND requests who did not receive peramivir had similar demographic characteristics and medical conditions (Supplementary Appendix Table S5).

Infection with influenza A virus was confirmed during hospitalization by real-time polymerase chain reaction or culture in 26 (84%) of the 31 treated patients; other diagnostic methods, such as immunofluorescence, were used for the other patients. In 23 cases, 2009 H1N1 subtype was confirmed; for the remaining cases, 2009 H1N1 subtype was epidemiologically presumed. In 1 case, influenza viral RNA was detected in extrapulmonary samples, including plasma and stool samples [22]. In another case, influenza A(H1N1) virus with the H275Y neuraminidase mutation was detected by pyrosequencing assay and confirmed by culture performed at the Centers for Disease Control and Prevention (L. Gubareva, personal communication).

A secondary bacterial pneumonia was documented in 3 patients (due to *Staphylococcus aureus*, *Enterobacter cloacae*, and an unspecified pathogen), all of whom died.

Treatment

Patients had been symptomatic for a median of 12 days (range, 3–30 days) and hospitalized for a median of 4 days (range, 1–24 days) prior to the initiation of peramivir and were treated for 1–14 days (median duration, 10 days). Most patients (27 [87%] of 31) had progressive disease despite NAI treatment either before or during hospitalization (Table 1; Supplementary Appendix Tables S1-S2), and 17 continued oseltamivir treatment after initiation of peramivir. Almost all patients (30 of 31) required mechanical ventilation, which often included the use of high-frequency oscillatory ventilation or extracorporeal membrane oxygenation (ECMO). In 13 (42%) of 31, influenza infection was complicated by acute renal failure, which required renal replacement therapy with hemodialysis, hemofiltration, or hemodiafiltration in 11 (35%) of 31 patients. In the majority of cases (55%), vasopressor support was also required.

Because this is the first report of peramivir treatment in children or pregnant/post-partum women, detailed information on the presentation, treatment, and clinical course of each of those patients is provided in Table 2.

Therapeutic drug monitoring was performed at the investigators' request in 7 adults and 4 children, 7 of whom required continuous renal replacement therapy (CRRT) (Supplementary Appendix Table S6). In previously reported results for 2 patients receiving CRRT [21] and in 5 other eIND patients, the clearance of peramivir was high and correlated with the degree of correction provided. An additional patient had 2 serum samples obtained; no additional information is available. In addition, an 11-year-old female patient (Figure 2) and a 15-year-old male

patient who were not undergoing dialysis and were treated with 10 mg/kg and 600 mg of peramivir daily, respectively, after failure of oseltamivir treatment had exposures similar to those observed in adults [14, 21, 23, 24]. In a 28-year-old, 4-day post-partum woman with disease progression despite 4 days of oseltamivir treatment who was not undergoing dialysis, peak drug levels were approximately one-third the average levels observed in healthy nonpregnant volunteers after treatment with peramivir 600 mg IV daily [14, 24] (Figure 3).

Outcome

Despite the severity of illness, survival at 14, 28, and 56 days after initiation of peramivir treatment was 76.7%, 66.7%, and 59.0%, respectively (Figure 4). In some cases, the primary cause of death was unresolved respiratory failure and adult respiratory distress syndrome (ARDS), but in other cases, death occurred because of the failure of other organ systems or complications reflecting underlying medical conditions (Table 3). Univariate analysis showed a significantly increased risk for mortality in men (odds ratio [OR], 6.87; 95% CI, 1.17–40.37; $P = .03$) and patients with higher APACHE II scores (OR, 1.14; 95% CI, 1.01–1.29; $P = .04$) (Table 4). No significant mortality effect of increasing age or time to peramivir treatment was observed in our small case series. However, the 10 pediatric patients and pregnant or post-partum patients who recovered received peramivir starting on hospital day 2–8, whereas the 4 patients who died received peramivir starting on hospital day 10–16 (Table 2).

Patients who recovered were discharged from the hospital after 8–117 days (median duration, 25 days). Peramivir treatment was generally well tolerated; no reports of serious adverse events or adverse events attributable to peramivir were received by BioCryst.

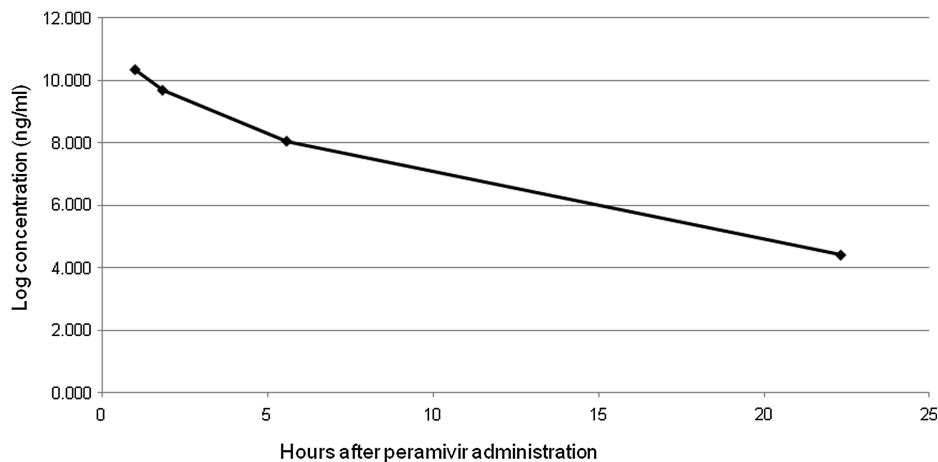


Figure 2. Semi-logarithmic concentration of peramivir over time after the second dose of 10 mg/kg/day in patient 8, an 11-year-old girl who recovered.

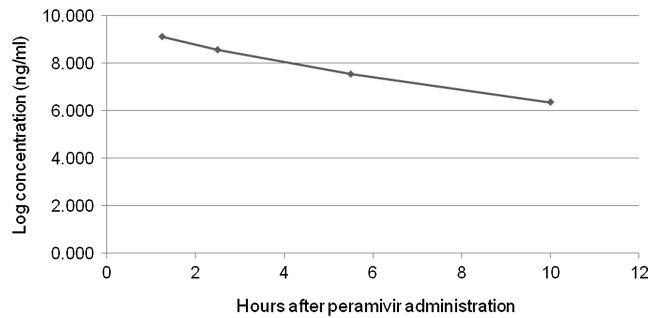


Figure 3. Semi-logarithmic concentration of peramivir over time after the third dose of 600 mg/day in patient 10, a post-partum woman who recovered.

DISCUSSION

In this review of hospitalized, critically ill patients with pandemic influenza, antiviral therapy with intravenous peramivir appears to have reduced mortality and to have been well tolerated. The uncontrolled nature of this observational report, however, makes assessment of efficacy and safety difficult. The data provide insight into the clinical impact and pharmacokinetics of peramivir in children, pregnant women, and patients with acute renal failure. The risk factors associated with mortality in this small series were more-severe disease and male sex, which are consistent with some previous reports [5, 25, 26].

This eIND experience represents the first report of peramivir administration in children, pregnant or post-partum women, and patients with acute renal failure, some of whom underwent TDM. The majority of patients in this 2009 H1N1-infected,

severely ill, hospitalized population were children and young, otherwise healthy adults, in contrast to the older population hospitalized during typical influenza seasons [2]. Obesity was seen in 35% of patients, and half of the obese patients were without other risk factors for severe disease, findings that are consistent with the wider experience with hospitalizations during the pandemic [2]. Pregnant women have been over-represented in the populations of patients hospitalized with 2009 H1N1 infection, often with rapidly progressive severe disease [2, 6]. Seven (64%) of 11 treated children and all pregnant or post-partum women survived in our case series. TDM in 2 pediatric patients who received 10 mg/kg to a maximum of 600 mg/day, which is a dose recommended on the basis of pharmacokinetic modeling, revealed peramivir exposures similar to those found in adults [14, 21, 23, 24], whereas peak drug levels in a post-partum woman were lower but were still far above the levels

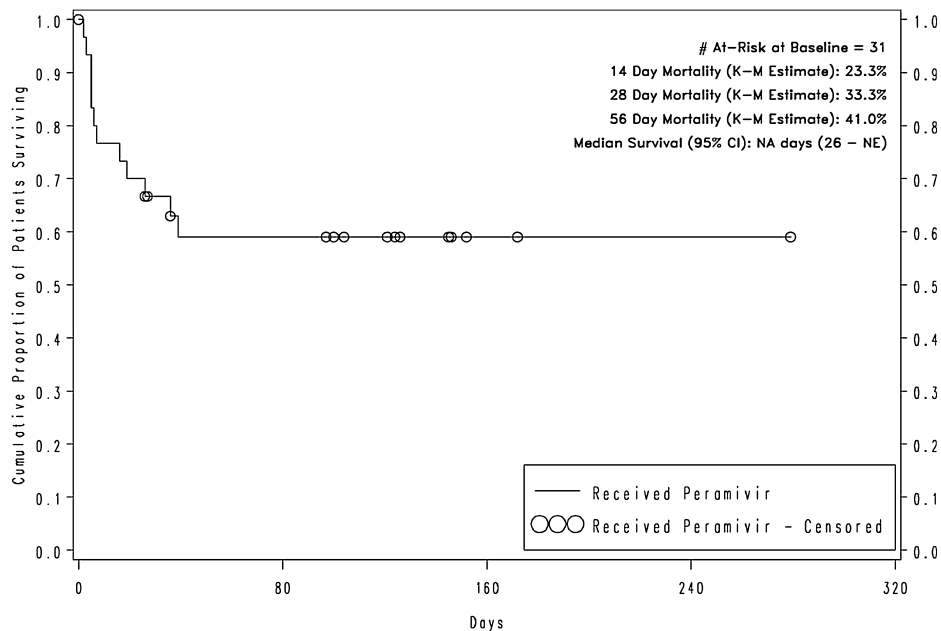


Figure 4. Kaplan-Meier survival curve.

Table 3. Primary Cause and Timing of Death for 12 Patients Who Died

Primary cause of death	Days after hospitalization	Days after peramivir start	Age, years
Acute lung injury, ARDS, MODS, pneumonia, renal failure	5	2	41
Heart failure, bacterial pneumonia, respiratory failure, kidney failure	6	4	18
Acute lung injury, ARDS, MODS, pneumonia	6	4	27
MODS, cardiac arrest, ARDS, pneumonia, MI, dysrhythmia, kidney and liver failure	10	1	55
Multi-organ failure, acute lung injury, ARDS, pneumonia, dysrhythmia, renal failure, encephalitis	12	4	53
Pneumonia, respiratory failure	12	5	76
Pneumonia, multi-organ failure	16	15	54
Viral and bacterial pneumonia, respiratory failure	19	9	14
Uncontrollable hemorrhage, MODS, DIC, shock, renal failure, vascular insufficiency, cholecystitis, decreased cardiac function	33	8 ^a	5
Global encephalopathy due to resuscitated cardiopulmonary arrest	34	25 ^a	8
Sepsis and bacterial pneumonia	37	35 ^a	38
Pneumonia, respiratory failure	53	38	13

NOTE. Primary cause of death according to the physician requesting intravenous peramivir. ARDS, adult respiratory distress syndrome; DIC, disseminated intravascular coagulation; MI, myocardial infarction; MODS, multi-organ dysfunction syndrome.

^a Medical support withdrawn at family request.

needed for influenza viral inhibition [14]. Additional studies are needed on the pharmacokinetics of peramivir in these subpopulations; higher dosages may be needed for patients during pregnancy and the early post-partum period.

As in previous reports [2, 3], renal failure was a complication of influenza infection, severe pneumonia, and ARDS in this case series and appears to have been associated with an increased risk of mortality. Because peramivir undergoes little metabolism in

Table 4. Risk Factors for Mortality in Peramivir-Treated Patients

Parameter	Alive(n=19)	Dead(n=12)	Odds ratio(95% CI)	P
Age, median years (range)	23 (0.3–51)	32 (5–76)	1.02 (0.98–1.07)	.25
Children <18 years of age	7/19 (37)	4/12 (33)	0.86 (0.19–3.92)	.84
Sex, M/F (% F)	8/11 (58)	10/2 (17)	6.87 (1.17–40.37)	.03
BMI, median value (range)	28.3 (12.5–44.2)	27.4 (15.9–50.0)	1.03 (0.94–1.12)	.52
BMI ≥ 30	6/19 (32)	5/12 (42)	1.55 (0.34–6.94)	.57
Immunocompromised ^a	4/19 (21)	3/12 (25)	1.25 (0.23–6.91)	.80
Lung disease	4/19 (21)	3/12 (25)	1.25 (0.23–6.91)	.80
Pregnant or post-partum	3	0		NA
Vasopressor support required	10/19 (53)	7/12 (58)	1.26 (0.29–5.42)	.76
APACHE II score, median value (range)	17 (5–36)	25 (16–37)	1.14 (1.01–1.29)	.04
APACHE II score ≥20	9/19 (47)	10/12 (83)	5.56 (0.95–32.46)	.06
Use of HFO/ECMO	7/19 (37)	6/12 (50)	1.71 (0.40–7.43)	.47
Use of CVVH/SLED/CVVHDF/CVVHD/CRRT	4/19 (21)	4/12 (33)	1.88 (0.37–9.57)	.45
Duration illness before peramivir, median days (range)	11 (3–26)	14 (5–29)	1.06 (0.93–1.21)	.40
Duration of hospitalization before peramivir, median days (range)	4 (1–24)	7 (1–15)	1.07 (0.93–1.22)	.37
Use of other NAIs	17/19 (89)	10/12 (83)	0.59 (0.07–4.85)	.62
Concomitant use of peramivir and oseltamivir	12/19 (63)	5/12 (42)	0.42 (0.10–1.83)	.25
Duration of illness before any NAI use, median days (range)	4.5 (-6 to 18)	7.0 (4–16)	1.12 (0.96–1.32)	.16
Duration of illness before oseltamivir or zanamivir use, median days (range)	4.0 (-6 to 18)	7.0 (4–14)	1.14 (0.93–1.41)	.20
Duration from other NAI use to peramivir use, median days (range)	4 (1–22)	4 (1–15)	1.01 (0.86–1.19)	.89

NOTE. Data are no. (%) or proportion (%) of patients, unless otherwise indicated. APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index, calculated as the weight in kilograms divided by the square of height in meters; CI, confidence interval; CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; HFO, high-frequency oscillation; SLED, slow low efficiency dialysis.

^aImmunocompromised patients were those having had prior chronic corticosteroid use, diabetes, chronic renal failure, solid-organ transplant, and/or hematopoietic stem cell transplantation.

humans and is eliminated unchanged in the urine, drug clearance correlates with creatinine clearance [27]. Our experience with 7 eIND patients and the experience of 2 patients treated under the EUA [23], all of whom had acute renal failure and TDM after dose adjustment of IV peramivir to dosages as high as 600 mg IV once daily, revealed no evidence of drug-induced toxicity and suggests a high clearance of peramivir by CRRT. Based on these results, current guidance includes dose adjustment according to the type and duration of CRRT provided [14]. Further study is needed to provide more-specific guidance for dose adjustment in subjects with acute renal failure, particularly those undergoing different modalities of renal replacement therapy, and such studies are ongoing.

Although not a statistically significant factor, earlier initiation of IV peramivir may have been associated with reduced mortality in the eIND cases, consistent with previous reports of the value of early intervention with NAI for both pandemic and seasonal influenza [2, 9, 10, 25]. The relationship of survival to early peramivir treatment was suggested in our population of pediatric and pregnant or post-partum patients. In all patients, most of the delay in delivering the drug was a delay in requesting peramivir after hospitalization (range, 1–24 days), not a delay in the acquisition of the drug after the eIND request was received. Delivery of drug could be shortened in future emergencies by distributing EUA stockpiles of intravenous NAIs, including peramivir, in multiple repositories across the country or in treating hospitals.

In this patient population with rapidly progressive viral pneumonia and other associated complications, including patients at high risk and at least 1 patient with the H275Y mutation in the NA gene, we documented a 59% survival rate 56 days after treatment with peramivir. The principal cause of death was often listed as respiratory failure and ARDS, but some patients died due to major organ failure or exacerbation of underlying conditions after the patient's viral pneumonia was resolved; antiviral therapy, particularly if it is applied late, would not be expected to impact such mortality. Despite the delay in peramivir initiation and the likely selection of the most-severely ill patients for peramivir treatment, the survival rate in our series is comparable to the 59%–86% survival of patients admitted to an ICU with confirmed or suspected 2009 H1N1 infection in early reports worldwide [3, 4, 25]. Taken together with the data from the Phase 2 study of peramivir [19], this suggests that peramivir is at least as effective as alternative regimens. Because most of the patients in this cohort had experienced a worsening condition despite oral antiviral therapy, systemic delivery of the antiviral in this unique but hard-to-study population may be a beneficial alternative.

The data from this population are consistent with previous reports of the clinical effects, safety, and tolerability of peramivir [8,17–19, 28]. In describing the FDA Adverse Event Reporting

System reports from 237 of the >1300 patients who received peramivir under the EUA from October 2009 through 23 June 2010, when the EUA expired, the authors concluded that it is unlikely that peramivir adversely affected outcomes [28].

Resistance to anti-influenza agents, including oseltamivir and zanamivir, is of increasing concern [29–31]. Clinical isolates expressing the H275Y mutation show high-level oseltamivir resistance (mean in vitro 50% inhibitory concentration [IC₅₀] ± standard deviation [SD], 679.5 ± 44.5 nM) and intermediate peramivir resistance (mean IC₅₀ ± SD, 36.5 ± 7.8 nM) without a change in zanamivir susceptibility [32]; the clinical significance of this finding, however, is not clear. In this series, we documented 1 patient with the H275Y mutation whose peramivir dose resulted in exposures above the reported IC₅₀ values [32, 33]. Data on the levels achieved in respiratory secretions, however, are lacking. The patient recovered, but the role of peramivir in that recovery is unclear, because serial viral samples were not analyzed and other interventions, including discontinuation of immunosuppressive medications and aggressive critical care support, may have contributed to his survival. Apparent clinical failure of IV peramivir therapy has been reported in an immunocompromised individual with oseltamivir-resistant 2009 H1N1 influenza A illness [34]. Zanamivir has also been delivered IV to treat cases of oseltamivir-resistant 2009 H1N1 infection [35], although it is not approved for this use, and it is the currently recommended therapy for patients with proven resistance secondary to the H275Y mutation [36].

Several patients in this series continued treatment with oseltamivir after IV peramivir was initiated. The combination of oseltamivir and peramivir was not associated with an increased risk of mortality. In vitro and in vivo animal studies and pharmacokinetic interaction studies in humans have not shown antagonism between oseltamivir and peramivir [13, 37, 38], although one report suggests antagonism between NAIs in vitro [39]. Combinations of antivirals with ≥2 different mechanisms of action have shown a trend toward improved clinical efficacy and reduced emergence of resistant variants in hospitalized subjects [40] and have been advocated to address the increasing antiviral resistance seen in circulating isolates [13, 37]. However, the current lack of available agents with different mechanisms of action warrants consideration of alternative approaches, such as the combination of NAIs [37].

Our report is limited by the small sample size and by both its observational and its uncontrolled nature. The selection of patients was affected by limited publicity about the eIND process and the lack of standard criteria for choosing those who would benefit from peramivir. Additionally, available data were limited; few patients had serial virologic or therapeutic drug monitoring, and not all relevant clinical data were collected.

In conclusion, these data represent a unique experience of the emergency treatment of adults and children with severe

influenza with IV peramivir. In this hospitalized population with viral pneumonia that had progressed despite other antiviral treatment, most patients survived after IV peramivir treatment. Although peramivir may have contributed to recovery in a number of these patients, well-controlled studies of peramivir for severe influenza are required to document the clinical and virologic efficacy of this novel agent, and these studies are ongoing.

Supplementary Material

Supplementary materials are available at *Clinical Infectious Diseases online* (http://www.oxfordjournals.org/our_journals/cid/).

Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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References

1. Johnson CE. Determination that a public health emergency exists. Available at: <http://www.flu.gov/professional/federal/h1n1emergency042609.html>. Accessed 15 September 2010.
2. Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. *N Engl J Med* **2010**; 362:1708–19.
3. Jain S, Kamimoto L, Bramley AM, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. *N Engl J Med* **2009**; 361:1935–44.
4. Dominguez-Cherit G, Lapinsky SE, Macias AE, et al. Critically ill patients with 2009 influenza A (H1N1) in Mexico. *JAMA* **2009**; 302:1880–7.
5. Centers for Disease Control and Prevention. Intensive-care patients with severe novel influenza A (H1N1) virus infection. Michigan, June 2009. *MMWR Morb Mortal Wkly Rep* **2009**; 58:749–52.
6. Jamieson DJ, Honein MA, Rasmussen SA, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* **2009**; 374:451–8.
7. Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. *JAMA* **2000**; 283:1016–24.
8. Kohno S, Kida H, Mizuguchi M, Shimada J. Efficacy and safety of intravenous peramivir for the treatment of seasonal influenza. *Antimicrob Agents Chemother* **2010**; 54:4568–74.
9. McGeer A, Green KA, Plevneshi A, et al. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clin Inf Dis* **2007**; 45:1568–75.
10. Lee N, Choi KW, Chan PK, et al. Outcomes of adults hospitalized with severe influenza. *Thorax* **2010**; 65:510–5.
11. Centers for Disease Control and Prevention. Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009–2010 season. Available at: <http://www.cdc.gov/h1n1flu/recommendations.htm>. Accessed 15 May 2010.
12. Uyeki T. Antiviral treatment for patients hospitalized with 2009 pandemic influenza A (H1N1). *N Engl J Med* **2009**; 361:e110 (ePub).
13. Bantia S, Parker CD, Ananth SL, Horn LL, Andries K, Chand P. Comparison of the anti-influenza virus activity of RWJ-270201 with those of oseltamivir and zanamivir. *Antimicrob Agents Chemother* **2001**; 45:1162–7.
14. Centers for Disease Control and Prevention. Emergency use authorization of peramivir IV fact sheet for health care providers. Available at: http://www.cdc.gov/h1n1flu/eua/pdf/final_hcp_fact_sheet_peramivirIV_CDC.pdf. Accessed 15 May 2010.
15. Bantia S, Kellogg D, Parker C, et al. A single intramuscular injection of peramivir demonstrates anti-influenza activity against recently isolated pandemic flu virus H1N1 (A/CA/04/2009). *Antiviral Res* **2010**; 86:A29.
16. Yoshida R, Kodama M, Kobayashi M, Kitano M, Sato A, Yamano Y. Therapeutic effect of peramivir (S-021812, BCX-1812) after single intravenous treatment of mice infected with influenza A and B viruses [abstract V-1065]. In: Program and abstracts of the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco). Washington, DC: American Society for Microbiology, 2009; 67.
17. Kohno S, Kida H, Mizuguchi M, et al. Intravenous peramivir for treatment of influenza A and B infection in high-risk patients. *Int J Infect Dis* **2010**; 14(suppl 1):e85–6.
18. Kohno S, Yen MY, Cheong JH, et al. Single-intravenous peramivir vs. oral oseltamivir to treat acute, uncomplicated influenza in the outpatient setting: a Phase III randomized, double-blind trial [abstract V-537a]. In: Program and abstracts of the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco). Washington, DC: American Society for Microbiology, 2009; 38.

19. Ison MG, McGeer AJ, Hui DS, et al. Safety and efficacy of multiple-day treatment with intravenous peramivir or oral oseltamivir in hospitalized adults with acute influenza [abstract V-6]. In: Abstracts of the XI International Symposium on Respiratory Viral Infections (Bangkok). New York, NY: The Macrae Group LLC, 2009.
20. Birnkrant D, Cox E. The emergency use authorization of peramivir for treatment of 2009 H1N1 influenza. *N Engl J Med* **2009**; 361:2204–7.
21. Bazan JA, Bauer KA, Hollister AS, et al. Pharmacokinetic monitoring of peramivir in two critically ill adult patients with 2009 H1N1 influenza A requiring continuous renal replacement therapy. *Pharmacotherapy* **2010**; 30:1016–20.
22. Campbell AP, Jacob ST, Kuypers J, et al. Respiratory failure caused by 2009 novel influenza A/H1N1 in a hematopoietic stem cell transplantation recipient: detection of extrapulmonary H1N1 RNA and use of intravenous peramivir. *Ann Int Med* **2010**; 152:619–20.
23. Thomas B, Hollister AS, Muczynski KA. Peramivir clearance in continuous renal replacement therapy [letter]. *Hemodial Int* **2010**; 14:336–40.
24. Beigel J, Harman LA, Collis PJ, et al. Pharmacokinetic and safety evaluations of escalating doses of peramivir administered intravenously in healthy volunteers [abstract A-1408]. In: Program and abstracts of the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago). Washington, DC: American Society for Microbiology, 2007.
25. Kumar A, Zarychanski R, Pinto R, et al. Critically ill patients with 2009 influenza A (H1N1) infection in Canada. *JAMA* **2009**; 302:1872–9.
26. Harms PW, Schmidt LA, Smith LB, et al. Autopsy findings in eight patients with fatal H1N1 influenza. *Amer J Clin Pathol* **2010**; 134:27–35.
27. Swan S, Marbury T, Smith W, et al. Safety and pharmacokinetics of peramivir following intravenous administration in subjects with renal impairment [abstract 623]. In: Program and abstracts of the 47th Annual Meeting of the Infectious Diseases Society of America (Philadelphia). Arlington, VA: IDSA, 2009; 73.
28. Sorbello A, Jones SC, Carter W, Struble K. the Peramivir Safety Team. [abstract V-648]. Program and abstracts of the 50th Interscience Conference on Antimicrobial agents and Chemotherapy (Boston).. Washington, DC: American Society for Microbiology, 2010.
29. Hurt AC, Holien JK, Parker M, Kelso A, Barr IG. Zanamivir-resistant influenza viruses with a novel neuraminidase mutation. *J Virol* **2009**; 83:10366–73.
30. Dharan NJ, Gubareva LV, Meyer JJ, et al. Infections with oseltamivir-resistant influenza A(H1N1) virus in the United States. *JAMA* **2009**; 301:1034–41.
31. Moscona A. Global transmission of oseltamivir-resistant influenza. *N Engl J Med* **2009**; 360:953–6.
32. Baz M, Abed Y, Boivin G. Characterization of drug-resistant recombinant influenza A/H1N1 viruses selected in vitro with peramivir and zanamivir. *Antiviral Res* **2007**; 74:159–62.
33. Boivin G, Goyette N. Susceptibility of recent Canadian influenza A and B virus isolates to different neuraminidase inhibitors. *Antiviral Res* **2002**; 54:143–7.
34. Memoli MJ, Hrabal RJ, Hassantoufighi A, Eichelberger MC, Taubenberger JK. Rapid selection of oseltamivir- and peramivir-resistant pandemic H1N1 virus during therapy in 2 immunocompromised hosts. *Clin Infect Dis* **2010**; 50:1252–5.
35. Dulek DE, Williams JV, Creech CB, et al. Use of intravenous zanamivir after development of oseltamivir resistance in a critically ill immunosuppressed child infected with 2009 pandemic influenza A (H1N1) virus. *Clin Infect Dis* **2010**; 50:1493–6.
36. Centers for Disease Control and Prevention. Antiviral treatment options, including intravenous peramivir, for treatment of influenza in hospitalized patients for the 2009-2010 season. Available at: http://www.cdc.gov/h1n1flu/EUA/peramivir_recommendations.htm. Accessed 15 May 2010.
37. Smee DF, Hurst B, Wong M-H, Tarbet EB, Babu YS, Morrey J. Efficacy of combinations of oseltamivir and peramivir in treating influenza a (H1N1) virus infections in cell culture and in mice. *Antiviral Res* **2010**; 86:A47.
38. Lasseter K, Atiee G, Baughman S, et al. Absence of pharmacokinetic (PK) interaction between intravenous (IV) peramivir and oral (PO) rimantidine or oseltamivir in humans [abstract A1-2001]. In: Program and abstracts of the 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (Boston). Washington, DC: American Society for Microbiology, 2010.
39. Nguyen JT, Hoopes JD, Le MH, et al. Triple combination of amantadine, ribavirin, and oseltamivir is highly active and synergistic against drug resistant influenza virus strains in vitro. *PLoS One* **2010**; 4:e9332. doi:10.1371/journal.pone.0009332.
40. Ison MG, Gnann JW Jr., Nagy-Agren S, et al. Safety and efficacy of nebulized zanamivir in hospitalized patients with serious influenza. *Antivir Ther* **2003**; 8:183–90.