Safety and efficacy of peramivir for influenza treatment

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Objective: This report presents a review of the efficacy and safety of peramivir, a neuraminidase inhibitor that was granted Emergency Use Authorization by the US Food and Drug Administration (FDA) from October 23, 2009 to June 23, 2010 during the 2009 H1N1 pandemic.

Methods: Literature was accessed via PubMed (January 2000–April 2014) using several search terms: peramivir; BCX-1812; RWJ 270201; H1N1, influenza; antivirals; and neuraminidase inhibitors. The peramivir manufacturers, Shionogi and Co Ltd and BioCryst Pharmaceuticals, were contacted to obtain unpublished data and information presented at recent scientific meetings. Information was obtained from the Centers for Disease Control and Prevention (CDC) and from US FDA websites. English-language and Japanese-language reports in the literature were reviewed and selected based on relevance, along with information from the CDC, US FDA, and the drug manufacturers.

Results: We obtained eleven clinical trial reports of intravenous peramivir, two of which described comparisons with oseltamivir. Seven of nine other recently reported published studies was a dose–response study. Clinical reports of critically ill patients and pediatric patients infected with pandemic H1N1 described that early treatment significantly decreased mortality. Peramivir administered at 300 mg once daily in adult patients with influenza significantly reduces the time to alleviation of symptoms or fever compared to placebo. It is likely to be as effective as other neuraminidase inhibitors.

Conclusion: Although peramivir shows efficacy for the treatment of seasonal and pH1N1 influenza, it has not received US FDA approval. Peramivir is used safely and efficiently in hospitalized adult and pediatric patients with suspected or laboratory-confirmed influenza. Peramivir might be a beneficial alternative antiviral treatment for many patients, including those unable to receive inhaled or oral neuraminidase inhibitors, or those requiring nonintravenous drug delivery.

Keywords: neuraminidase inhibitor, pandemic, pH1N1, avian flu, antiviral therapy, drug resistance

Introduction

Influenza, an acute febrile respiratory illness, is caused by influenza A or B virus. It occurs in outbreaks each year, mainly during winter. Signs and symptoms of upper and/ or lower respiratory tract involvement are common. Two major classes of antivirals are licensed for the treatment and prevention of influenza: M2 inhibitors and neuraminidase inhibitors (NAIs).[1,2] The latter prevent the destruction of sialic acid-bearing receptors that are recognized by influenza A and B virus hemagglutinins which, in turn, prevents the virus from being released from infected cells and from passing through respiratory secretions to initiate new cycles of replication.[3,4] NAIs are active against both influenza A and B, although adamantanes, which include amantadine and rimantadine, are

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active only against influenza A.[4] The Advisory Committee on Immunization Practices does not recommend adamantanes for influenza treatment because of an increase in resistant isolates in the United States.[5,88]

Peramivir, classified with oseltamivir and zanamivir among the NAIs, was developed by BioCryst Pharmaceuticals, Inc. (Birmingham, AL, USA) for the treatment of influenza infection.[6,7] Peramivir has significantly stronger binding affinity to the NA enzyme than either oseltamivir or zanamivir. Moreover, peramivir inhibits influenza A and B viruses, including influenza virus strains that might be resistant to other NAIs.

Oseltamivir is orally administered. Zanamivir and laninamivir are inhaled. By contrast, peramivir is the first intravenously administered NAI. Oral or inhalant administration to young children is difficult with peramivir, thereby limiting its treatment benefits. However, the availability of an intravenously administered NAI is expected to be especially important for treating patients who cannot take or tolerate oral or inhaled anti-influenza agents, such as young infants.

Intravenous administration of zanamivir or peramivir provides rapid drug delivery at high levels. It might affect the host's endogenous NA.[8] In March 2007, BioCryst Pharmaceuticals, Inc. and Shionogi & Company Ltd (Osaka, Japan) entered an exclusive license agreement to develop and commercialize peramivir in Japan for the treatment of seasonal and potentially life-threatening human influenza.[9]

Peramivir was emergently released during the pandemic of 2009 (April 3, 2009–August 31, 2010).[10] Phase III clinical trials in Japan, Taiwan, and South Korea have demonstrated that intravenously administered peramivir is not inferior to oral oseltamivir for the treatment of adult patients with seasonal influenza A or B.[11] From January 2010, peramivir was licensed for use in adults. Since October 2010, it has also been available in Japan for children, including neonates, with influenza infection.[10] It has therefore been used in advance of the rest of the world, becoming available immediately after Phase III clinical trials in Japan. Its use has demonstrated that intravenously administered peramivir is safe and clinically and virologically effective for children with pH1N1 infection.[12] Adult patients were also administered peramivir, but the pediatric peramivir preparation was almost too late for pandemic patients. In August 2010, peramivir was approved by the Korean Food and Drug Administration (KFDA).[13] Peramivir is available in Japan as Rapiacta™ (Shionogi &

Company Ltd) and in South Korea as PeramiFlu™ (Green Cross Corporation).[13]

Zanamivir and oseltamivir, which were approved in 1999, have since become commonly used in the US. Intravenously administered peramivir was granted Emergency Use Authorization (EUA) by the US FDA for the treatment of influenza in selected patients in the US based on favorable results of a multinational clinical trial approved in 2010.[14] This EUA was the first to be issued for an unapproved drug. The grant, however, expired on June 23, 2010, when the pandemic ended.[14] Many otherwise healthy children and adults, as well as high-risk patients in Japan with influenza virus infection, are currently treated with four NAIs: oseltamivir; zanamivir; laninamivir; and peramivir. The clinical effectiveness of peramivir has not yet been evaluated sufficiently in patients with influenza. This review describes the status of the research and clinical trials of peramivir for the treatment of pH1N1 influenza and/or seasonal influenza during the postpandemic of 2009, and explains its potential to support therapeutic strategies for influenza virus infection.

Objective

This review was undertaken to present information about the clinical efficacy and safety (including adverse events [AEs]) of peramivir for the treatment of naturally acquired influenza. Clinical reports presenting data from placebo-controlled randomized trials and single-group studies were reviewed, along with regulatory comments and reviews of the safety and efficacy of peramivir for influenza in patients of all ages. This evaluation assesses related issues for at-risk and otherwise healthy populations.

Methods
Data sources and search strategy
A literature search was conducted using PubMed (US National Library of Medicine, Bethesda, MD, USA) (January 2000–March 2014) and the Cochrane Database (The Cochrane Collaboration, Oxford, UK) (January 2000 March 2014) with the following search terms: peramivir; BCX-1812; RWJ 270201; influenza; H1N1; antivirals; and NAIs. The peramivir manufacturers (Shionogi & Company Ltd and BioCryst Pharmaceuticals, Inc.) were contacted to solicit unpublished data and information presented at recent scientific meetings. Additional information was obtained from Clinicaltrials.gov, the Centers for Disease Control and Prevention (CDC), and FDA Websites. Literature review

articles were searched using PubMed and were referenced for this review.

Study selection and data extraction

Available English-language and Japanese-language reports were selected and reviewed, as was information from the CDC, FDA, and the Ministry of Health, Labour, and Welfare (Tokyo, Japan). The requirements for EUA for peramivir were also consulted.

Only published reports of trials that examined the use of peramivir, or those which evaluated peramivir versus placebos or another NI (oseltamivir) for the treatment of seasonal or pH1N1 influenza in healthy adults, children, elderly people, or at-risk individuals were considered. No search was performed before 2000 because peramivir (RWJ-270201/BCX-1812) was first introduced as a novel NAI for influenza in 2000. Experimental and clinical studies conducted in animal models such as mouse, ferret, equine, and macaque with influenza infections were considered. Clinical studies published in languages other than English or Japanese were excluded.

Results

Table 1 shows that we obtained eleven clinical trial reports. Reports of nine studies of peramivir in dose–response or placebo-controlled studies were found in the Cochrane Database of Systematic Reviews.[15] We collected these reports and combined them with others from the clinicaltrials.gov Website (http://www.clinicaltrials.gov/), irrespective of whether they had been published or not. Details are presented in Table 2. We divided the results into four eras depending on the time when the trials were initiated: prepandemic development; prepandemic; pandemic; and postpandemic 2009.

Clinical efficacy
Prepandemic development

Eleven reports of Phase I, Phase II, and Phase III clinical trials examining the clinical efficacy and safety of peramivir treatment for influenza patients have been published (Table 1). These trials were performed during the eras of prepandemic and pandemic 2009. Preclinical studies and murine pharmacodynamic studies demonstrated high selectivity and efficacy of peramivir against both influenza A and B strains.[22] In Phase I clinical trials, oral peramivir dosages of 0.5–800 mg/kg/day once daily for 10 days were well tolerated.[16,17,19] Once-daily administration of peramivir was supported based on analyses of pharmacodynamics and

effectiveness, for which we measured the time necessary for viral clearance in Phase II studies.[17] Hayden et al[18] reported a Phase I study using peramivir in influenza virus-infected patients, but a full description of the trial is not available. Two double-blind, placebo-controlled trials were conducted to ascertain the appropriate dosage with several dose regimens in subjects who had been infected experimentally with influenza A/Texas/36/91 or B/Yamagata/16/88 viruses. In these studies, 400 mg administered orally once daily significantly reduced nasal wash virus titer. A second study showed that an oral loading dosage of 400 mg or 800 mg and 800 mg once daily was effective in reducing viral titer.[19] Symptoms were not significant in either group. Peramivir of 400–800 mg appeared to be well tolerated by these patients.[19] Barroso et al[20] conducted randomized, controlled dose–response trials for the treatment of experimental human influenza. For the trials, 288 healthy adults were inoculated with influenza A or B. Oral peramivir treatment with dosages of 400 mg once daily for 5 days significantly reduced the viral titer of influenza A. Both 400 mg and 800 mg once daily for 5 days reduced the titer of influenza B, as defined by the area under the curve values.[20] Clinical trials of orally administered peramivir were conducted first.[22] Peramivir showed low oral bioavailability. Expecting effects in other drug delivery routes, trials were designed to ascertain whether intravenously or intramuscularly administered peramivir can reduce viral titer, and to assess the time to alleviate influenza symptoms.[21] The drug was developed as an intravenously administered preparation. Other Phase I, Phase II, and Phase III trials are described elsewhere.[19,22]

Prepandemic era
Clinical studies of healthy adults

The safety and efficacy of peramivir treatment in patients with uncomplicated seasonal influenza virus infection were first evaluated in dose–response studies. A placebo-controlled, double-blind Phase II study[23] demonstrated that, compared with placebo, a single intravenous dose of peramivir at either 300 mg (hazard ratio: 0.681; adjusted P=0.0092) or 600 mg (hazard ratio: 0.666; adjusted P=0.0092) significantly reduced the duration of influenza symptoms for adult influenza outpatients, irrespective of the influenza virus subtype or the duration of symptoms before the study (Table 1). A randomized, double-blind Phase III study[11] comparing single-dose intravenously administered peramivir with oral oseltamivir in uncomplicated patients with seasonal influenza was conducted in Japan, Taiwan, and

Table 1 Summary of clinical trials of peramivir treatment in patients with influenza virus infection

Trial	Cohort (age)	Type	Study design	Number of subjects	Primary outcome
Phase I	Healthy adults	Seasonal flu A and B	1 mg/kg, 2 mg/kg, 4 mg/kg, and 8 mg/kg BID or placebo for 10 days.	84	Pharmacokinetics and safety.
Phase I	Elderly, ≥65 years of age	Seasonal flu A and B	Intravenous peramivir on day 1; thereafter, two cohorts of eight subjects each (six peramivir, two placebo) received 4 mg/kg BID for either 5 days or 10 days. Up to 800 mg/kg/day for 10 days.	20	Safety and pharmacokinetics.
Phase I	Hospitalized with uncomplicated influenza ≥19 years of age	Seasonal flu A and B	A single-center, crossover, uncontrolled, open-label study after intramuscular and intravenous administration of a single dose of 75 mg, 150 mg, or 300 mg of peramivir.	27	Concentrations in the secretion of peramivir; a similar reduction in viral titers observed after 48 hours.
Phase II	Adults with positive influenza A or B (by RIDT)	Seasonal flu A and B	Randomized, double-blind, placebo-controlled, multicenter administration of a single dose of 150 mg or 300 mg of peramivir or placebo (as an intramuscular single dose) within 48 hours of symptom onset.	344	Time to the alleviation of symptoms.
Phase II	Adults with positive influenza A or B (by RIDT) with symptom duration ≤48 hours	Seasonal flu A and B	Randomized, double-blind, placebo-controlled, multicenter administration of a single dose of 600 mg of peramivir or placebo as an intramuscular single dose.	402	Time to the alleviation of symptoms.
Phase II	Hospitalized with uncomplicated influenza	Influenza A (H1N1), A (H3N2) or B	Randomized to 5 days of treatment with either peramivir (400 mg or 200 mg) administered once daily or oral oseltamivir (75 mg).	137	Reduction in viral titers observed after 48 hours.
Phase III	≥6 years of age; hospitalized	2009 A (H1N1)	Open-label randomized trial, 5–10 days treatment with intravenous 300 mg twice daily or 600 mg once daily peramivir.	234	Time-weighted change in influenza virus titer from screening/baseline to 48 hours, as measured by $log10$ TCID50.
Phase II	Outpatient; 20–64 years	Seasonal flu A and B	Randomized, double-blind, placebo-controlled trial; a single dose of intravenous peramivir (300 mg or 600 mg) or a matching placebo.	298	Time to alleviation of symptoms from the start of treatment.
Phase III	Uncomplicated influenza ≥20 years of age	Seasonal flu A and B, influenza A (H1N1), A (H3N2) or B	A three-armed, multicenter, randomized, double-blind, multinational study. A single dose of intravenous peramivir (either 300 mg or 600 mg) was compared to a 5-day regimen of 75 mg of oral oseltamivir BID.	1,091	Time to alleviation of symptoms from the start of treatment.

Results	Conclusions	First author	Reference/detailed description	Location/sponsor/ trial number
Reduction of the plasma concentration of peramivir was similar across all dose groups. No serious adverse events occurred.	Up to 8 mg/kg/day for 1–10 days might be well tolerated.	Beigel	112	US/BioCryst Pharmaceuticals, Inc./ BCX1812-101, -102, -103
No evidence of drug accumulation over either 5 days or 10 days.	In the elderly group, acceptable safety profile with the multiple-day, twice-daily intravenous administration of peramivir	Collis	113	US/BioCryst Pharmaceuticals, Inc./ BCX1812-104
Concentrations of peramivir were found to exceed the IC50 values for influenza A and B strains for up to 24 hours for each dose.	Peramivir inhibited the replication of the influenza virus during this period.	Alexander	114	US/BioCryst Pharmaceuticals, Inc./ BCX1812-103
No statistically significant differences between treatment groups for the time to alleviation of symptoms (primary endpoint) Improvement over placebo was 22.9 hours with the 150 mg dose and 21.1 hours with the 300 mg dose.		NA	115	US, Australia, Canada/ BioCryst Pharmacueticals, Inc./NCT00419263
No statistically significant differences between treatment groups for the time to alleviation of symptoms (primary endpoint). The median time to alleviation was 91.1 hours for a 600 mg intramuscular Injection of peramivir and 106.1 hours for placebo.	Peramivir is generally safe and well tolerated.	Atiee	116	US, Australia, New Zealand, South Africa/ BioCryst Pharmaceuticals, Inc./NCT00705406
Titers of influenza A viruses in nasopharyngeal specimens decreased in a similar manner, but more rapid decreases in titers of influenza B with peramivir were noted.	Treatment of acute seasonal influenza in hospitalized adults with either peramivir or oseltamivir, resulting in generally similar clinical outcomes.	Ison	26	US, Australia, Canada, Hong Kong, New Zealand, Singapore, South Africa/ BioCryst Pharmaceuticals, Inc./NCT00453999
Viral titers declined without differences.	Once- or twice-daily administration was associated with decreases in viral shedding and clinical improvement.	Ison	24	US, Australia, Canada, New Zealand, Mexico, Puerto Rico/BioCryst Pharmaceuticals, Inc. and US DHHS/NCT00957996
Peramivir significantly reduced the time to alleviation of symptoms when compared with placebo.	A single intravenous dose of peramivir is effective and well tolerated.	Kohno	23	Japan/ Shionogi & Company, Limited/0722T062 1
The median durations of influenza symptoms were 78.0 hours, 81.0 hours, and 81.8 hours in the groups treated with 300 mg of peramivir, 600 mg of peramivir, and oseltamivir.	300 mg and 600 mg peramivir groups were not inferior to the oseltamivir group. A single intravenous dose of peramivir may be an alternative to a 5-day oral dose of oseltamivir for patients with seasonal influenza virus infection.	Kohno	11	Japan, South Korea, Taiwan/ Shionogi & Company, Limited/0815T06 31

(Continued)

Table 1 (*Continued*)

Trial	Cohort (age)	Type	Study design	Number of subjects	Primary outcome
Phase III	Influenza patients at high risk of serious complications	Seasonal flu A and B influenza A (H1N1), A (H3N2) or B	Uncontrolled double-blind, multicenter, administered intravenous peramivir over multiple days at 300 mg/day or 600 mg/day.*	37	Time to alleviation of symptoms from the start of treatment.
Phase III	≥28 days to <16 hospitalized	2009 A (H1N1)	Multicenter, open-label, uncontrolled study; 10 mg/kg (600 mg maximum) of intravenous peramivir once daily for up to 5 days.	106	Efficacy, safety, and pharmacokinetics of a single intravenous dose of peramivir in children.

Note: *The duration of administration was adjusted (up to 5 days) on a case-by-case basis, depending on the patient's temperature and clinical condition.
Abbreviations: BID, twice daily; IC50, 50% inhibitory concentration; RIDT, rapid influenza diagnostic test; TCID50, tissue culture-infective dose 50; US DHHS, United States Department of Health and Human Services; NCT, National Clinical Trial; NA, not applicable as not yet published.

South Korea. The median durations of influenza symptoms were 78.0 hours, 81.0 hours, and 81.8 hours, respectively, in groups treated with 300 mg of peramivir, 600 mg of peramivir, and 75 mg oseltamivir, orally twice a day. The fever lasted for <34 hours in patients treated with peramivir, but 37 hours in patients treated with oseltamivir, as shown in Figure 1, demonstrating that peramivir is not inferior to oseltamivir for treating seasonal influenza A and B (Table 1).[11] A Phase III study comparing oseltamivir to intravenously administered zanamivir in hospitalized patients is underway.[24]

Clinical studies of people at high risk for developing flu-related complications

The safety and efficacy of peramivir use were evaluated for patients under CDC-defined high-risk conditions: children younger than 5 years old, but especially children younger than 2 years old; adults 65 years of age and older; and pregnant women.

Dose–response study of high-risk adults

In a multicenter, uncontrolled, randomized, double-blind Phase III study,[25] 300 mg or 600 mg of peramivir was administered intravenously once daily for 1–5 days, depending on the disease condition, to 37 adult influenza patients who were at high risk of developing severe flu-related complications. The hazard ratio (90% confidence interval [CI]) for the 600 mg group compared to the 300 mg group was 0.497 (90% CI: 0.251–0.984). The median duration of influenza illness was 68.6 hours (90% CI: 41.5–113.4) overall. The 42.3-hour (90% CI: 30.0–82.7) result for the 600 mg group was significantly shorter than the 114.4-hour (90% CI: 140.2–235.3) result in the 300 mg group (Table 1).[25]

Ison et al[26] conducted a multinational Phase II randomized, double-blind trial in seven countries to evaluate the efficacy and safety of intravenously administered peramivir compared to oral oseltamivir in 2007–2008, the prepandemic era. The 137 adult hospitalized patients with suspected acute seasonal influenza were randomized to 5-day treatments with intravenously administered peramivir (400 mg or 200 mg once daily) or oral oseltamivir (75 mg twice daily). The median time (95% CI) to clinical stability was 24.3 hours (95% CI: 21.2–47.5) with peramivir 400 mg, 31.0 hours (95% CI: 17.2–47.7) with peramivir 200 mg, and 35.5 hours (95% CI: 23.3–37.9) with oseltamivir (*P*=0.541). No significant difference was found among the three treatments (Table 1).[26] However, a Phase III, multicenter, randomized, double-blind, controlled study to evaluate the efficacy and safety of intravenously administered peramivir and standard care compared to standard care alone in adults and adolescents hospitalized for severe influenza was terminated by the study's Data Monitoring Committee because of futility.[24,27]

Dose–response study of children

Table 1 shows two studies that specifically examined the safety and efficacy of peramivir treatment in children: one study examined 106 children in one Phase III trial;[12] 234 patients including four adolescents (12–17 years of age) were examined in the other Phase III trial.[24] No other reports describe clinical trials of peramivir in children.[28] Relevant information for ongoing clinical trials sponsored by Bio-Cryst Pharmaceuticals, Inc. is available at the clinicaltrials. gov Website.

The five completed, three terminated, three withdrawn, and one unknown trials among the 12 trials are shown and summarized based on the Cochrane Database Systematic

Results	Conclusions	First author	Reference/detailed description	Location/sponsor/ trial number
The overall median duration of influenza illness was 68.6 hours. The duration of illness was significantly shorter in the 600 mg group than in the 300 mg group.	The efficacy of single and multiple intravenous doses of peramivir is comparable to oseltamivir. Potentially useful for high-risk patients.	Kohno	25	Japan/Shionogi & Company, Limited/ 0816T06 32.
The median time to the alleviation of influenza symptoms was 29.1 hours. Virus-positive children decreased to 10% on day 6.	Peramivir is clinically and virologically effective and safe in children with pH1N1 virus infection.	Sugaya	12	Japan/ Shionogi & Company, Limited/0918T0633

Review, with modification in Table 2.[15] Detailed reviews of trials conducted during this period are also available.[21,22,29]

Pandemic 2009

The emergence of the influenza pandemic led to new guidelines that recommended antiviral treatment for all adults hospitalized with influenza, including pregnant women. Those guidelines were published on December 7, 2009 and were accepted on January 1, 2010.[30] The EUA allowed health care providers to use peramivir, subject to stringent conditions.[14]

A few patients received peramivir or intravenously administered zanamivir, for which the FDA had issued the EUA for treatment of severe pH1N1 infections during the pandemic (from September 2009 through to June 23, 2010). Many peramivir recipients treated under the EUA were critically ill and at risk for influenza-related complications. Detailed reviews for the trials conducted during this period are available in the literature.[21,22,28,29]

In a dose–response study of high-risk patients, an open-label randomized trial was conducted on 234 hospitalized patients over 6 years of age, predominantly with pH1N1.[24] Patients were randomized to groups receiving 300 mg twice daily or 600 mg once daily of intravenously administered peramivir. Changes in nasopharyngeal viral titers from baseline to 48 hours were evaluated, as was the time to clinical resolution. No significant difference in clinical or virological effects was found between the groups (Table 1).[24]

The efficacy and safety of intravenously administered peramivir has been demonstrated in children with the 2009 influenza A (H1N1) virus infection. Sugaya et al[12] conducted a multicenter, open-label, uncontrolled study to investigate the efficacy, safety, and pharmacokinetics after the once-daily intravenous infusion of 10 mg/kg (600 mg maximum) of

peramivir in 106 pediatric patients infected with the pH1N1 virus, as confirmed by polymerase chain reaction. Results showed equal effectiveness of peramivir in all age groups. The median time to the alleviation of symptoms was 29.1 hours (95% CI: 22.1–32.4). The proportion of the 106 children who were virus-positive was 78.2% on day 2 after the start of treatment. It had decreased to 7.1% on day 6 after the treatment.[12] For pH1N1 virus infection, the efficacy and safety in children were expected to be similar to those in adults. This clinical report is the first of a study conducted with children.[12]

Approximately 60.8 million cases, 274,304 hospitalizations, and 12,469 deaths are estimated to have occurred in the US because of pH1N1.[31] In the US, peramivir was used under EUA for hospitalized patients who had been infected with pH1N1. Data show that 1,274 patients (median age: 43 years; range: 0–92 years; 49% male) received ≥1 dose of peramivir for 6 days of median duration.[32] Therefore, approximately 0.46% of hospitalized patients might have been treated with peramivir based on the estimated 274,304 hospitalizations attributable to pH1N1. A clinical study evaluating the efficacy and safety of peramivir treatment among hospitalized adults and children with influenza was done in the US.[14] All subjects received peramivir under EUA. Only some clinical data have been published (Table 3).

Shrestha et al[31] estimated that pH1N1 deaths occurred in people younger than 65 years of age, with children and working adults having risks for hospitalization and death that were 4–7 times and 8–10 times greater, respectively, than the estimates for seasonal influenza in the years from 1976–2001.

Antiviral treatment increased during the pandemic. Doshi et al[33] compared antiviral use among adults hospitalized with influenza before and during the pandemic from

Table 2 Clinical trials of peramivir in dose–response or placebo-controlled studies

NCT number	Reference	Study details	Current primary outcome	Subjects	Intervention	Study status	Notes
00297050	Not provided	A Phase I, double-blind, placebo-controlled, dose-escalating study to evaluate the safety and tolerability of intravenous administration peramivir.	Not provided.	18–50 years old	Drug: peramivir	Completed	Dose-ranging study
00957996	Ison et al[24]	A Phase III, open-label, randomized study of the antiviral activity, safety, and tolerability of intravenous peramivir in hospitalized subjects with confirmed or suspected influenza infection.	Change (reduction) in influenza virus titer, as measured by the log10 TCID50.	18 years and older	Parallel assignment: 300 mg twice daily, and 600 mg once daily	Completed	Peramivir study; does not have placebo/do nothing comparator
01063933	Not provided	Phase I and Phase II; a pharmacokinetic/pharmacodynamic and safety evaluation of investigational intravenous peramivir in children with influenza disease (CASG 117).	Peramivir dose that provides the AUC 24 between 60 µg hour/L and 94 µg hour/L.	Up to 17 years	Drug: peramivir	This study was withdrawn prior to enrollment	Pharmacokinetics study
00419263	Not provided	A Phase II, multicenter, randomized, double-mask, placebo-controlled study to evaluate the efficacy and safety of intramuscular peramivir in subjects with uncomplicated acute influenza.	To evaluate the efficacy of peramivir administered intramuscularly as compared to placebo.	18 years and older	Peramivir 150 mg, 300 mg, or placebo	Completed	
00453999	Ison et al[26]	A Phase II, multicenter, randomized, double-mask, double-dummy study comparing the efficacy and safety of peramivir administered intravenously once daily versus oseltamivir administered orally twice daily in adults with acute serious or potentially life-threatening influenza.	Time to resolution of clinical signs of acute influenza in hospitalized patients.	18 years and older	Parallel assignment: 200 mg or 400 mg of peramivir, or oral oseltamivir phosphate (75 mg twice daily)	Completed	
00486980	Not provided	A Phase III multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of intramuscular peramivir in subjects with uncomplicated acute influenza.	Not provided.	18 years and older	Peramivir: 150 mg or 300 mg	This study was withdrawn prior to enrollment	

NCT	Sponsor	Study description	Outcome measure	Age/population	Intervention	Status	Notes
00610935	Not provided	A Phase III multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of intramuscular peramivir in subjects with uncomplicated acute influenza.	The time to alleviation of the clinical signs and symptoms of influenza.	18–75 years	Peramivir, placebo	Terminated	
00705406	Not provided	A Phase II, multicenter, randomized, placebo-controlled study to evaluate the efficacy and safety of intramuscular peramivir 600 mg in subjects with uncomplicated acute influenza.	To evaluate the efficacy of peramivir administered intramuscularly compared to placebo on the time to alleviation of clinical symptoms in adult subjects with uncomplicated acute influenza.	18 years and older	600 mg of peramivir or placebo	Completed	
00958776	Not provided	A Phase III, multicenter, randomized, double-blind, controlled study to evaluate the efficacy and safety of peramivir administered intravenously in addition to providing standard care as compared to standard care alone in adults and adolescents who are hospitalized for serious influenza.	Measurement of vital signs and oxygen saturation will be summarized by visit; changes from baseline.	12 years and older	Peramivir 600 mg (adults); peramivir 10 mg/kg (adolescents)	Terminated	A Phase III study of intravenous peramivir in hospitalized patients was stopped by its DSMB because of futility: http://investor.shareholder.com/biocryst/releasedetail.cfm?ReleaseID=719562.[27]
01224795	Not provided	A Phase III, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of intravenous peramivir in subjects with uncomplicated influenza.	The efficacy of peramivir administered intravenously was compared to placebo on the time to alleviation of clinical symptoms with acute uncomplicated influenza. The time to alleviation of clinical symptoms in adolescents and adults with uncomplicated acute influenza measured from patient-reported study diaries.	Adults (≥18 years), adolescents (12 years to <18 years)	Drug: peramivir Adults: 600 mg administered intravenously. Adolescents: 10 mg/kg (not to exceed a maximum dose of 600 mg), administered intravenously	Terminated	
01146353	Not provided	An observational cohort study.	The primary outcome measure will be to determine the sieving coefficient for peramivir.	Hospitalized adults (18 years and older) undergoing continuous renal replacement therapy	Drug: peramivir	Withdrawn prior to enrollment	Sponsor: Midwestern University

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Abbreviations: NCT, National Clinical Trial; TCID50, tissue culture-infective dose 50; AUC24, area under the curve at 24 hours; DSMB, Data and Safety Monitoring Board.
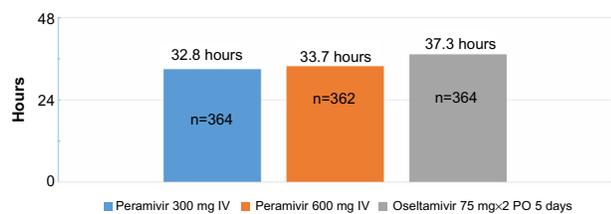
Figure 1 Mean duration of fever after onset.
Notes: The median time required for patients' body temperatures to return to normal (ITTI) is shown. Analyzed using a Cox proportional hazards model. The ITTI returned to a normal temperature (<37°C), and it remained for more than 12 hours. Copyright ©2013 Shionogi & Co., Ltd. Adapted from Fever lasting for less than 34 hours in patients treated with peramivir [pamphlet]. Osaka: Shionogi & Co., Ltd.; 2013.[10] Data are from a multinational, randomized, double-blind Phase III study in Japan, Taiwan, and South Korea.[11]
Abbreviations: ITTI, intent-to-treat infected; n, number; IV, intravenous; PO, per os.

data collected via medical record reviews of patients aged ≥18 years admitted during the prepandemic and pandemic eras in ten states. When compared to use in prepandemic seasons, antiviral treatments of hospitalized adults increased from 54% to 82%, especially in pregnant women, for whom treatments increased from 22% to 86% during the pandemic.[33] Fry et al[34] reported the frequency and characteristics of patients who received NAI based on surveillance data in areas that included 22 million adults and children from selected counties in ten states, representing approximately 7% of the US population. The results showed that 46,216 patients (80%) had documented receipt of an NAI. Among those who received an NAI, 0.2% of children and 1% of adults received an NAI intravenously, 33 received peramivir (one child), and eight received zanamivir intravenously (two children).[34] Very few people had been given peramivir.

Hernandez et al,[35] on behalf of BioCryst Pharmaceuticals, Inc., which provided peramivir under FDA Emergency Investigational New Drug (eIND) regulations, first characterized 20 adults and eleven children who received peramivir at the beginning of the pandemic based on data collected using a standardized case report from April–October 2009: all patients had pneumonia with respiratory failure; 30 of 31 required mechanical ventilation; 17 continued oseltamivir treatment after peramivir initiation; and 12 patients died because of major organ failure or the exacerbation of underlying conditions. Early peramivir treatment was related to higher survival in the population of pediatric, pregnant, or postpartum patients. Results showed that ten patients who recovered received peramivir starting on hospital day 2–8, although the four patients who died received peramivir starting on hospital day 10–16.[35] Jain et al[36] reported that these data cannot be related to the effectiveness of intravenously administered peramivir in severely ill persons infected with influenza because most of them (87%) received concurrent oseltamivir, and there was no comparison group. Patients had

been hospitalized for a median of 4 days (range, 1–24 days) before the initiation of peramivir, and they had been treated for 1–14 days (median duration, 10 days). Patients who recovered were discharged from the hospital after 8–117 days (median duration, 25 days).[35] The median time from symptom onset to peramivir treatment was not described. It is difficult to ascertain the precise effect of peramivir. Further studies must assess its clinical effectiveness and safety because peramivir recipients under the EUA were critically ill and were at high risk for influenza-related complications.[37,38]

Early treatment was ideal, but it was difficult to initiate antiviral drug use in facilities that had a request under the EUA. Randolph et al[39] reported that only 5.8% (49 of 838) of patients had received antiviral medications before pediatric intensive care unit (PICU) admission. Louie et al[37] examined 784 influenza patients under 18 years of age who had been hospitalized in intensive care units (ICUs), and they additionally described 57 critically ill adults and pediatric patients treated with peramivir for pH1N1 virus infection in California. The median (range) time from symptom onset to antiviral treatment out of the total number of patients who received peramivir (number [n] =57), fatal patients (n=29), and nonfatal patients (n=28) were, respectively, 4 days (0–23 days), 5 days (0–23 days), and 4 days (0–9 days). The median (range) time from symptom onset to peramivir treatment of the total peramivir patients (n=57), fatal patients, and nonfatal patients were, respectively, 9 days (2–38 days), 10 days (2–36 days), and 9 days (2–38 days). The high mortality rate, approximately 50%, was attributed to the pre-existing clinical severity of cases before the request for peramivir.[37]

The pH1N1-related PICU mortality rates were 7%–39% in Canada, Australia, New Zealand, and Argentina.[40–42] Independent risk factors associated with fatal outcomes have not been well established because of smaller sample sizes.[38,39,43,44] Critically ill patients with a median age of 40 years (5 months to 81 years) with pH1N1 virus infection in California were also evaluated. In all, 29 (51%) of the 57 hospitalized peramivir recipients in the ICUs died. The median time from symptom onset to peramivir treatment was 8 days (1–22 days). The 10 days (2–36 days) noted among fatal cases were not compared with the 9 days (2–38 days) among the nonfatal cases. High mortality rates might not be attributable to late peramivir treatment, but rather to the pre-existing clinical severity level; greater deterioration of the patient's condition occurred following oral oseltamivir treatment in ICUs.[37] Louie et al[43] reported that antiviral treatment was significantly associated with decreased mortality (odds ratio =0.38; 95% CI: 0.17–0.87). Children treated earlier in their illness were less likely to die than those who

were treated later. In particular, antiviral treatment within 48 hours of illness onset was significantly associated with survival (P=0.04). The results suggest that prompt treatment with NAIs might improve the survival of children who are critically ill with influenza.[43] Antiviral drugs are expected to be most effective within 48 hours from symptom onset.[44] Further investigations must evaluate the safety and effectiveness of peramivir in hospitalized and critically ill patients.

Postpandemic 2009

The pH1N1 influenza virus has moved into the postpandemic period. Localized outbreaks of various magnitudes continue every year as seasonal influenza.

The world's first approval of peramivir was granted by the Ministry of Health, Labour and Welfare in Japan in late January 2010, so that its intravenous administration would benefit many influenza patients.[45,46] Peramivir was approved by the Korean FDA in August 2010.

Because the EUA expired on June 23, 2010, when the pandemic ended, peramivir is only currently available in Japan and South Korea. Postmarketing product surveillance demonstrated that the clinical efficacy of peramivir is not inferior to that of other NAIs for the treatment of seasonal influenza (Figure 1).[11] Results obtained from some clinical studies show that peramivir is more effective in alleviating influenza symptoms than are other NAIs (Table 3).[39,47] After the pandemic, a few retrospective clinical studies of adults and children were performed only in Japan, where peramivir has been used at the discretion of physicians since its approval on January 2010.[38,39,43,47] In a retrospective observational study conducted during the 2010–2011 influenza season, 263 pediatric influenza patients receiving oseltamivir, zanamivir, laninamivir, or peramivir were analyzed. In A (H3N2)-infected patients, the median duration of fever in the oseltamivir group was 3.3 times longer than in the peramivir group (P=0.0303). Peramivir treatment is likely to show its greatest effectiveness in reducing the duration of symptoms.[48] Similar results were obtained from a retrospective study performed between February–April 2011.[49] The effectiveness of treatment with NAIs (oseltamivir, peramivir, laninamivir, and peramivir) was assessed in 223 patients aged 5–18 years who had been diagnosed as having influenza A (131) or B (92) infection; this was diagnosed by the rapid influenza diagnostic test. The median duration of fever after treatment with peramivir (1 day) was significantly shorter than that after treatment with zanamivir (2 days) in influenza A patients (P=0.0283). The median duration of fever after peramivir treatment (1 day) was significantly shorter than after laninamivir treatment (3 days) in influenza B patients (P=0.0097).[49] A retrospective

study[50] recently showed the clinical features of hospitalized adults and children with influenza who were treated with peramivir during the 2012–2013 season. The clinical efficacy of peramivir was evaluated in 32 hospitalized adult influenza patients with underlying diseases, and the treatment was administered within 48 hours of disease onset – either 300 mg of peramivir administered once daily or 75 mg of oseltamivir administered for 5 days twice daily during 2012–2013. The treatment was chosen by the physician in accordance with the patient's medical condition. No significant difference was found between the peramivir (30.9 hours) and oseltamivir (34.7 hours) groups in terms of the median time to defervescence.[50] Peramivir appeared to be as efficacious as oseltamivir. These studies were retrospective, nonrandomized, without placebo, not controlled, and with a small sample size. The studies were performed only to compare the effects among NAIs. Although not of high quality, these studies underscore the clinical effectiveness of peramivir, which had already been demonstrated during its nationwide use in many facilities in Japan when used within 48 hours of disease onset.[111]

Clinical safety
Adverse effects of neuraminidase inhibitors
Adverse effects of NAIs in uncomplicated adult patients are typically mild.[51] Nausea and vomiting have been the most conspicuous adverse effects in oseltamivir trials in healthy adults.[52,53] No significant adverse effects were recorded in treatment trials with zanamivir in healthy adults.[15,52] In children and at-risk individuals treated with oseltamivir or zanamivir, no significant drug-related or severe adverse effects were found.[53] Zanamivir can cause acute bronchospasm and severe declines in respiratory function among patients with or without a previous history of asthma or chronic obstructive pulmonary disease, although the frequency is not clear.[54,55] For one trial, Wang et al[56] described study results whereby gastrointestinal symptoms were related to the adverse effects of laninamivir treatment in children. Other AEs, including neuropsychiatric AEs were observed occasionally in influenza patients receiving oseltamivir.[57,58] Sudden death was reported as an AE related to oseltamivir.[59,60] The effects of influenza infection itself and/or drug–disease interactions should be considered. However, for the US and Japan, neuropsychiatric AEs were reported significantly less often during the pandemic than during the previous influenza seasons.[51]

Adverse effects of peramivir
Uncomplicated adults
Kohno et al conducted a dose-ranging Phase I study of intravenously administered peramivir at up to 800 mg once daily

Table 3 Characteristics of clinical studies of peramivir for the treatment of adult and pediatric patients with influenza infection

Year	Type	Study design	Age	N	Subjects	Intervention/treatment
Adults						
2014	2012–2013 seasonal flu A and B	Retrospective cohort	>18 years	32	Inpatient	300 mg intravenously administered once daily for 1 day versus oral oseltamivir (75 mg) twice daily for 5 days
2013	2009 A (H1N1)	Open-label randomized trial	≥18 years	234	Inpatient	300 mg intravenously administered twice daily or 600 mg once daily for 5 days
2013	2009 A (H1N1)	Randomized, double-blind, placebo-controlled trial	≥18 years	137	Inpatient	Intravenous 400 mg or 200 mg once daily, or oral oseltamivir (75 mg twice daily) for 5 days
2011	2008–2009 season; seasonal flu A and B	Randomized, double-blind study	≥20 years	1,091	Both (coexisting disease at baseline; 34.9%–40.3% in each group)	Intravenous 300 mg or 600 mg once daily for 1 day versus placebo
2011	Seasonal flu A and B	Per protocol set	≥20 years	37	High-risk inpatient	Intravenous 300 mg or 600 mg once daily for 1–5 days
2010	Seasonal flu A and B	Randomized, double-blind, placebo-controlled trial	20–64 years	300	Outpatient	300 mg or 600 mg once daily for 1 day
Children						
2012	2009 A (H1N1)	Multicenter, open-label, uncontrolled study	≥28 days to <16 years	106	Inpatient	Intravenously administered 10 mg/kg (600 mg maximum) once daily
2012	2009 A (H1N1) and A (H3N2)	Observational study	8.8±3.9 years	263 (oseltamivir =104; peramivir =4)	Outpatient	Intravenously administered 10 mg/kg (600 mg maximum) once daily
2012	2011 seasonal flu A and B	Retrospective chart review	0–18 years	Total: 223 (influenza A) (5–18 years); oseltamivir =83; peramivir =22. Influenza B (5–18 years): laninamivir =13; peramivir =13	Outpatient	Intravenously administered 10 mg/kg (300 mg maximum) once daily
2011	2009 A (H1N1)	Retrospective chart review	≤15 years	1,000 (four received peramivir); 660 (66.0%) had no underlying Illness.	Inpatient	Not described
Critically ill/at-risk adults and children						
2013	2009 A (H1N1)	Retrospective chart review	0–17 years	784 (unknown N treated with peramivir)	Inpatient	Of the 784 patients, 653 (83%) were treated with NAIs
2012	2009 A (H1N1)	Retrospective chart review	<1–90 years	Total: 344 (<18 years: 28; 18–65 years: 290; >65 years: 21)	Inpatient	The median duration of peramivir administration was 5 days (range: 1–14 days)

Results	Conclusion	First author	References
Median TTRF: 300 mg once-daily intravenous peramivir treatment group versus The 5-day oseltamivir treatment group (30.9±18.7 hours versus 34.7±18.6 hours; P=0.62).	The clinical efficacy of peramivir is not inferior to that of oseltamivir.	Yoshino	50
Median TTAS: 600 mg once peramivir treatment group (135 hours; 95% CI: 89–184 hours) versus 300 mg twice-daily peramivir group (158 hours; 95% CI: 103–306 hours). Median TTRF: 600 mg once peramivir treatment group (27 hours; 95% CI: 13–37 hours) versus 300 mg twice-daily treatment group (24 hours; 95% CI: 13–54 hours).	600 mg once-daily or 300 mg twice-daily administration was associated with decreases in viral shedding and clinical improvement.	Ison	24
Median TTAS: 400 mg 5-day peramivir treatment group (24.3 hours; 95% CI: 21.2–47.5 hours) versus the 200 mg 5-day peramivir group (31.0 hours; 95% CI: 17.2–47.7 hours) versus the 75 mg twice-daily 5-day oseltamivir group (35.5 hours; 95% CI: 23.3–37.9 hours); P=0.541.	Peramivir and oseltamivir results were generally similar.	Ison	26
Median TTAS: 300 mg once-daily intravenous peramivir treatment group (78.0 hours; 95% CI: 68.4–88.6 hours), 600 mg once-daily intravenous peramivir treatment group (81.0 hours; 95% CI: 72.2–91.5 hours), and 5-day oseltamivir treatment group (81.8 hours; 95% CI: 73.2–91.1 hours).	The peramivir groups were noninferior to the oseltamivir group.	Kohno	11
Median TTAS: overall, 68.6 hours (90% CI: 41.5–113.4 hours); 300 mg group, 114.4 hours (90% CI: 40.2–235.3 hours); 600 mg group, 42.3 hours (90% CI: 30.0–82.7 hours).	Peramivir appears to be a potentially useful treatment for high-risk patients.	Kohno	14
300 mg once-daily peramivir treatment group, 59.1 hours (95% CI: 50.9–72.4 hours); HR *0.681 (95% CI: 0.511–0.909); 600 mg group, 59.9 hours (95% CI: 54.4–68.1 hours). HR* 0.666 (95% CI: 0.499–0.890).	Single intravenous dose of peramivir is effective and well tolerated.	Kohno	23
Median TTAS: 29.1 hours (95% CI: 2.1–32.4 hours); median TTRF: 20.6 hours (95% CI: 19.4–21.1 hours).	Peramivir is clinically and virologically effective and safe in children with pH1N1 virus infection.	Sugaya	12
Median TTRF: zanamivir treatment group (23.0 hours; 95% CI: 22.0–24.0 hours) versus the peramivir group (17.0 hours; 95% CI: 7.2–26.8 hours).	Peramivir treatment group (17.0 hours; 95% CI: 7.2–26.8 hours) was significantly shorter than that in the oseltamivir treatment group (P=0.044).	Shobugawa	48
Median TTRF: oseltamivir treatment group (2 days) versus peramivir group (1 day; P=0.0242) in influenza A. Laninamivir group (3 days) versus peramivir group (1 day; P=0.0097) in influenza B.	No significant difference for any of the other combinations of the drug/disease type/age groups.	Hikita	49
In 88.9% of the patients, treatment with neuraminidase inhibitors was initiated within 48 hours after the onset of illness. One patient died of H1N1/09 infection.	Low mortality rate attributable to the universal implementation of early treatment with neuraminidase inhibitors.	Sugaya	106
Of 653 NAI-treated cases, 38 (6%) died, as compared with eleven (8%) of the 131 untreated cases (odds ratio =0.67; 95% CI: 0.34–1.36).	Prompt (<48-hour) treatment with NAIs may improve the survival of critically ill children.	Louie	43
76 (60%) patients were improved, eleven (9%) were unchanged, seven (6%) had deteriorated but not died, and 30 (24%) had died.	Rash was the only treatment-emergent adverse event attributable to peramivir. Safety data were insufficient.	Sorbello	38

(Continued)

Table 3 (*Continued*)

Year	Type	Study design	Age	N		Subjects	Intervention/treatment
2012	2009 A (H1N1)	Retrospective comparative analysis with or without peramivir	5 months to 81 years	57		Inpatient	Comparative analysis: 1) critically ill patients who received peramivir and critically ill patients who were treated with NAIs but who did not receive peramivir; 2) fatal and nonfatal peramivir-treated cases
2012	2009 A (H1N1)	Retrospective report review	0–92 years	1,274		Inpatient	Received peramivir through the EUA program

Abbreviations: N, number; TTRF, time to resolution of fever; TTAS, time to alleviation of influenza symptoms; CI, confidence interval; HR, hazard ratio; NAIs, neuraminidase inhibitor; EUA, Emergency Use Authorization.

for 6 days in healthy adults.[23] Results showed that peramivir was well tolerated (Kohno et al, unpublished data, 2010). The authors evaluated the safety of a single dose of peramivir for otherwise healthy influenza outpatients. For the study, 1,091 patients with seasonal influenza A and B were randomized into one of three groups: single intravenous infusion of 300 mg; 600 mg of peramivir; or matching placebo. Severe AEs occurred with two subjects. One patient in the 300 mg group had a prolonged QT interval on electrocardiogram. The other had increased blood creatinine in the 600 mg group. Both AEs were regarded as related to the study medications. Both of these events resolved without treatment. The other severe AEs were attributed to influenza virus infection or its complications, most commonly gastrointestinal symptoms. In the 300 mg, 600 mg, and placebo groups, diarrhea occurred, respectively, in 14.1%, 15.2%, and 17.0%, and nausea in 3.0%, 6.1%, and 1.0%.[23]

High-risk adults and children

In the uncontrolled, double-blind, randomized Phase III trial[25] of intravenously administered peramivir (300 mg/day or 600 mg/day) for 1–5 days described previously, two of 18 patients were administered 300 mg and 19 patients were administered 600 mg of peramivir among 37 high-risk adult patients with seasonal influenza A or B infection. One patient developed bacterial pneumonia, and another developed pneumonia.[25] In an uncontrolled double-blind, multicenter Phase III study of uncomplicated 1,091 adult influenza patients, the incidences of severe AEs, respectively, accounted for 5.2%, 8.2%, and 6.6% of cases in the intravenous 300 mg peramivir, 600 mg peramivir, and oral oseltamivir groups. No difference in the incidence of severe AEs or adverse drug reactions was found among the treatment groups. The most common severe AEs were a prolonged QT interval and a decreased neutrophil count. The incidences of a prolonged QT interval and a decreased neutrophil count in the peramivir

groups were similar to those in the oseltamivir group. In many of these patients, the lowest neutrophil count was observed on day 3 of peramivir administration. This count recovered more rapidly than in the oseltamivir group. The incidence of severe adverse reactions in either peramivir group was not different from that of the oseltamivir group.[11]

In a multinational Phase II study of 137 hospitalized adult patients in the 2007–2008 season conducted by Ison et al[26] (and described in the results, and in Table 1 and 3), the overall incidences of AEs were 52%, 56%, and 41%, respectively, in the groups treated with 400 mg or 200 mg of peramivir or 75 mg of oseltamivir. The incidence was higher in the peramivir groups than in the oseltamivir group, mainly because of the frequency of diarrhea, but the incidence of severe adverse reactions in either peramivir group resembled that in the oseltamivir group.[26]

The reports that will be described next are related to the situation of the pandemic. Hernandez[35] reported data for 31 patients who had received peramivir for 2–15 days. No general or severe AEs were attributable to peramivir.[35] Sorbello et al[38] evaluated the safety of intravenously administered peramivir for suspected or confirmed pH1N1 virus infection. Safety surveillance was limited because clinical reports were submitted to the US FDA Adverse Event Reporting System. The FDA safety team analyzed reports submitted to the Adverse Event Reporting System. From October 23, 2009 to June 23, 2010, data were processed for at least 1,274 patients who received ≥1 dose of peramivir. A report of 344 patients (median age 45 years [<1–90 years], including 28 children and three pregnant women) described rash as the only treatment-emergent AE attributable to peramivir. The high mortality rate (15%; 53 of 344 patients) and the development of acute respiratory distress syndrome (7%; 25 of 344 patients) were likely to account for part of the severity of the patients' influenza A infection. Renal failure (5%; 17 of 344 patients) was commonly reported, probably

Results	Conclusion	First author	References
29 (51%) peramivir recipients died. Peramivir recipients were more likely to die ($P \leq 0.0001$). Nonfatal recipients versus fatal recipients: shorter length of hospital stay (median: 16 days versus 31 days, respectively; $P=0.002$). Nonfatal recipients received peramivir sooner after their disease onset than fatal recipients did. (7 days versus 9 days; $P=0.02$).	Before receiving peramivir, peramivir recipients were in a more serious condition than untreated patients were. Further study in randomized controlled trials is needed.	Louie	37
Approximately 1,274 hospitalized patients received peramivir.	Peramivir treatments are available for pH1N1-hospitalized patients.	Yu	32

because peramivir has a high rate of renal excretion. Death and renal failure were unlikely to have affected outcomes adversely because many patients were critically ill and had independent risk factors for flu-related complications. In view of the uncertainties related to the safety information reporting system, the authors were unable to estimate the incidence of AEs.[38]

Pediatric patients

Sugaya et al[12] described 116 AEs in 73 (62.4%) of the 117 patients with pH1N1 infection enrolled in the Phase III study described in the section "Dose–response study of children". The data showed that 107 AEs occurred in 67 (62.6%) of the 107 patients who received a single dose; nine AEs occurred in six (60.0%) of the ten patients who received two doses. Of 117 patients, 45 events in 34 patients (29.1%) might have been related to the drug, and they were regarded as adverse drug reactions. Many AEs were mild or moderate. Most AEs were gastrointestinal disorders: diarrhea (16.2%); vomiting (11%); and a decrease in neutrophil count (21.4%). Psychiatric disorders such as abnormal behavior were found in 2.6% of subjects (Table 1).[12]

Randolph et al[39] reported the clinical characteristics of children with pH1N1 infection admitted to a PICU in the US; 2.5% of 838 children with pH1N1 admitted to the PICU received peramivir. Patients who received peramivir had already been regarded as having a high risk of death (relative risk: 6.0; range: 3.6–9.9). No severe AEs related to peramivir were reported. Children with pre-existing neurologic conditions and immune compromise were at increased risk of pH1N1-associated death after PICU admission.[39] Most of the available safety data indicated that the single-dose use of peramivir in adults and pediatric outpatient populations commonly led to AEs that reportedly included diarrhea, nausea, vomiting, and neutropenia.[12,61,62] Available data related

to AEs of multiple-dose peramivir in critically ill patients are scarce.[37]

Recommendations and difficulties of intravenous peramivir based on previous reports

Peramivir-resistant virus

The two major classes of antivirals for the treatment and prevention of influenza are M2 inhibitors and NAIs. The M2 inhibitors amantadine and rimantadine, which only act on influenza A viruses, are not pertinent in clinical use against circulating seasonal H3N2 and (H1N1) pdm09. Moreover, all H7N9 and many H5N1 strains are resistant to the M2 inhibitors.[63]

An NAI binds to an influenza virus' NA, inhibiting the enzyme's activity. When NA proteins of viruses change, NAIs lose their ability to bind to and inhibit the function of the virus' NA. A particular genetic mutation of the NA prevents NAIs from inhibiting NA activity, thereby producing a resistant virus.[64] Resistant viruses have been isolated from oseltamivir-treated adult patients and from natural environments with no apparent history of drug exposure.[65] The H274Y mutation confers resistance to oseltamivir and peramivir, but not to zanamivir. Mutations at I222 and R292 can also reduce peramivir sensitivity. McKimm-Breschkin[63] reviewed the details of viral mutations and their relative susceptibility to NAIs. In early studies,[66–71] in which the viruses were primarily seasonal H1N1 strains, oseltamivir-resistant H274Y mutant viruses were isolated from patients after treatment or prophylaxis with oseltamivir or peramivir, and also from untreated patients. During the winter of 2007–2008, an oseltamivir-resistant seasonal influenza A (H1N1) strain with an H274Y mutation emerged in the northern hemisphere[72,73] and rapidly spread around the world.[74–76] During the pandemic, a resistant A/H1N1 virus (Russian strain) was displaced by the pH1N1 virus sensitive to NAIs. To date, oseltamivir resistance

remains low among the circulating influenza viruses in the world. Approximately 0.5%–1.0% of community pH1N1 isolates are currently resistant to oseltamivir or peramivir.[63] The H275Y mutation in pH1N1 was associated with a high level of resistance to oseltamivir. It conferred an intermediate level of resistance to peramivir.[77,78] A cluster of 14 cases of influenza B viruses with an I222V mutation conferring reduced susceptibility to both oseltamivir and peramivir has also been reported recently.[79] In addition, the R292K mutation confers a very high level of resistance to oseltamivir, and intermediate resistance to peramivir.[80] The H275Y mutation was associated with a high level of resistance to oseltamivir. It conferred an intermediate level of resistance to peramivir.[77,78]

Takashita et al[81] recently reported that six viruses possessed an H275Y substitution in the NA protein, which conferred cross-resistance to oseltamivir and peramivir during November and December 2013. Furthermore, McKimm-Breschkin et al[82] characterized human H1N1 influenza isolate A/Hokkaido/15/02, which had hemagglutinin and NA mutations that reduce drug susceptibility to oseltamivir, zanamivir, and peramivir. Two viruses had a NA Y155H mutation that reduced its susceptibility to all NAIs. One virus had both the Y155H mutation and a hemagglutinin D225G mutation. The authors also isolated the third mutant virus, which had both NA V114I and hemagglutinin D225N mutations. This report is the first to describe a demonstration of a specific hemagglutinin mutation that is correlated with reduced drug susceptibility.[82]

Two patients became infected with a sensitive virus first, and subsequently became infected with a virus which was resistant to both osertamivir and peramivir but sensitive to zanamivir, probably because of rapid selection.[77] Viral isolates collected from the patients on day 0 included the wild-type virus. The resistant viruses with a H275Y mutation were isolated at 9 days and 14 days of therapy. All other isolates that were collected after those days included the resistant virus conferring H275Y. After the initial diagnosis was made, an enteral antiviral treatment including peramivir was administered to two patients with suspected viral replication that had been prolonged for 44 days in one patient and for 46 days in the other. Both patients experienced overall improvements in their symptoms.[77] Reportedly, one effect of the continuous administration of intramuscular antiviral treatment was the reduction of the fatality rate for immunosuppressed mice infected with influenza A (H1N1) 2009 virus.[78] Once infected with the resistant virus, as described earlier in this section, monitoring of the resistant virus and research for a treatment strategy must be continued.

Antiviral treatments are widely used in many adults and children in Japan. Table 4 shows that higher levels of

Table 4 Influenza antiviral drug resistance in Japan versus the US during the 2013–2014 flu season

Antivirals	A (H1N1) pdm09			A (H3N2)			B		Total
	Oseltamivir, peramivir	Zanamivir, laninamivir	Amantadine	Oseltamivir, peramivir	Zanamivir, laninamivir	Amantadine	Oseltamivir, peramivir	Zanamivir, laninamivir	
Japan[a]									
Resistant virus strain (%)	103 (4.2)	0	43	0	0	4 (100)	0	0	
Analyzed number	2,446	302	43	163	163	4	214	214	3,549
Reported number	3,401			1,681			2,862		7,944
US[b]									
Resistant virus strain (%)	59 (1.2)	0		0	0		0	0	59
Analyzed number									5,100

Notes: Data from: [a]http://www.nih.go.jp/niid/ja/flu-m/flutoppage/2068-flu-flu-dr/4775-flu-dr-20140623.html;[117] [b]http://www.cdc.gov/flu/weekly/summary.htm.[118]

resistance to oseltamivir and peramivir in Japan are likely to be attributable to their heavier usage than in the US. Emergent resistance during treatment is still uncommon. Global surveillance must be continued.

Avian influenza viruses

Since November 2003, more than 600 sporadic cases of human infection with highly pathogenic avian influenza (HPAI) A (H5N1) virus have been reported, mainly in Asian countries and Egypt.[83] Other subtypes of avian influenza A viruses have been reported: HPAI A (H7N3) virus in Mexico since June 2012;[84] and variant influenza A (H3N2) viruses in the US since July 2011.[85] Since the first human case of reassortant avian-origin influenza A (H7N9) virus was reported in Shanghai, People's Republic of China in March 2013,[86] more than 400 cases of human A (H7N9) virus infection have been reported through April 2014.[87] Health officials worldwide are becoming increasingly alarmed about the influenza virus' resistance to NAIs.

During the 2009 H1N1 pandemic, a reduction in disease severity by the early administration of NAIs was observed.[88] In addition, the early administration of NAIs was effective against HPAIA (H5N1) infection in Egypt.[89] Data related to human infections with seasonal, pandemic, and HPAIA (H5N1) viruses indicated that the earlier an antiviral treatment is initiated, the greater the clinical benefit.[90] Little is known about the clinical effect of a NAI on A (H7N9) virus. However, in the laboratory, oseltamivir showed a reduction of mortality in A (H7N9)-infected mice, and administration within 48 hours from disease onset was more effective.[91] According to a report of the clinical courses of 111 cases of A (H7N9) infection in the People's Republic of China, 97.3% of patients were administered peramivir or oseltamivir, but only 10% of them were administered within 48 hours from the onset of the infection. Therefore, the efficacy is unclear. Patients with A (H7N9) virus infection were highly complicated with respiratory failure and pneumonia.[92] Considering these results, the CDC recommended early oral or enterical administration of oseltamivir for uncomplicated influenza, hospitalized patients, or severe or complicated cases because oseltamivir has been used widely to date.[93] Early intravenous administration of peramivir has been recommended in the Japanese Interim Guidance for avian influenza A (H7N9) virus infections in humans.[94] The optional administration of peramivir should be investigated in future studies.

The CDC guidance suggests a twofold (10-day) extended administration period of NAIs as an option in severe cases.

In uncomplicated cases with A (H7N9) virus infection, drug administration is suggested to last 5 days.[95] The viral sequence data indicate susceptibility to NAIs, except for an R292K mutation in the NA protein of the A/Shanghai/1/2013 virus.[90] In the People's Republic of China, oseltamivir treatment was unsuccessful in patients with A (H7N9) virus infection. Resistant virus conferring mutations in the NA gene was detected in patients with severe respiratory failure.[96] The policy regarding NAI recommendation remains unchanged because few cases have been observed, but future studies must survey changes carefully.

Treatment of peramivir

Peramivir has been used at the dosage suggested by the CDC, as based on results from Phase II and Phase III trials conducted with the intravenous administration of single 300 mg or 600 mg doses of peramivir treatment, which showed statistically significant effects compared to placebo in adult patients with acute uncomplicated influenza.[22,62] The standard adult dose of peramivir is 600 mg, which is administered intravenously once daily for 5–10 days. However, the single 300 mg or 600 mg dosage of intravenously administered peramivir might be an alternative to a 5-day oral dosage of oseltamivir for patients with uncomplicated seasonal influenza.[11] A retrospective study that did not use randomized placebo-controlled trials showed that the clinical efficacy of peramivir was not inferior to that of oseltamivir.[50]

A Phase III trial of peramivir administered intravenously to hospitalized patients for 1–5 days showed that the influenza illness duration was significantly shorter in the 600 mg group than in the 300 mg group.[25] A large, open-label, randomized trial showed no significant clinical or virological difference between 300 mg of peramivir administered intravenously twice daily and a 600 mg dose administered once daily for 5 days.[24] Other clinical trials show that the administration of peramivir at doses of 400 mg or 200 mg once daily and 300 mg twice daily for 5 days are treatment options.[24,26] In children, single doses of 10 mg/kg (600 mg maximum) of intravenously administered peramivir for 1 day is effective both clinically and virologically in an open-label, uncontrolled study. Despite the scarcity of safety and efficacy data (Table 3), intravenously administered peramivir appears to be effective for pediatric patients.[48,49]

A Policy Statement of The Japanese Association for Infectious Diseases[97] recommends the early administration of intravenously administered peramivir for uncomplicated or hospitalized adult and pediatric patients, including those who are unable to receive inhaled or oral NAIs. Recom-

mended doses for patients with impaired renal function are available.[62,63]

The 2013–2014 CDC guidance for the use of influenza antiviral drugs remains unchanged from last season because high susceptibility to oseltamivir and zanamivir during the 2012–2013 flu season continues.[63,95]

Resistant viruses have evoked concern in Japan, where NAIs are used most. Treatment of NAI-resistant virus-infected children has yielded poor results. Hosoya et al most highly recommended the once-daily administration of 10 mg/kg of peramivir for 5 consecutive days in the official website of Japan Pediatric Society.[98] In a macaque model infected with HPAIA (H5N1), repeated peramivir administration (30 mg/kg/day once a day for 5 days) starting immediately after infection significantly reduced viral titers in the upper respiratory tract ($P<0.05$).[99] These results provide supportive evidence for the repeated administration of peramivir to highly pathogenic avian influenza virus infection.

The 2013 Interim Guidance for humans infected with the avian influenza A (H7N9) virus is expected to be helpful for the use of antiviral drugs in the treatment of human infections with avian influenza A (H7N9).[93] It is crucially important to administer an antiviral agent as soon as possible, even in uncomplicated patients. Higher doses with longer treatment regimens might be necessary in immunosuppressed persons, although the clinical benefit is unknown.[93] Table 5 presents the peramivir treatment parameters based on the evidence presented earlier.

Rapid diagnosis and early antiviral treatment

Observational data from the pH1N1 pandemic suggest that there is an association of early antiviral treatment and increased survival, even for children, pregnant women, and severely ill patients.[100–103]

Influenza can be fatal in children, thereby underscoring the importance of recommending that all children receive antiviral treatment as early as possible.[104] Therefore, the 2013–2014 guidance recommends early antiviral treatment by oseltamivir or zanamivir for any patient with confirmed or suspected influenza who is hospitalized; has severe, complicated, or progressive illness; or who is at higher risk of complications (age <2 years old or those with a medical condition).[95]

Peramivir, which is suitable for critically ill patients under 2 years of age, and for others who cannot receive oral antiviral treatment and who need only intravenous administration, is anticipated as a treatment option based on the favorable results of recent clinical trials.[24,26]

Clinics and hospitals commonly use rapid diagnostic tests. Most people with an influenza-like illness in Japan are tested and treated with an appropriate choice of antiviral drugs if

Table 5 Recommendation of intravenous peramivir use for the treatment of influenza

Subjects	Dosage	Duration	Reference for guidance or underlying data for recommendation
Severe or complicated hospitalized, high-risk patients			
Adults (≥18 years)	Single 300 mg or 600 mg dose	5–10 days	Centers for Disease Control and Prevention
	300 mg twice daily or 600 mg once daily	5 days	Ison et al[24]
	400 mg or 200 mg once daily	5 days	Ison et al[26]
	300 mg or 600 mg once daily (600 mg is better)	1–5 days	Kohno et al[11]
	300 mg or 600 mg once daily	1–5 days	Kohno et al[25]
Uncomplicated adults			
Adults	300 mg or 600 mg	1 day	Kohno et al[11]
Children			
Children	(mg/kg)	Initial treatment courses of 5 days or 10 days are permitted	Centers for Disease Control and Prevention
Birth through 30 days	6 mg/kg		
31 days through 90 days	8 mg/kg		
91 days through 180 days	10 mg/kg		
181 days through 5 years	12 mg/kg		
6 years through 17 years	10 mg/kg		
	The maximum daily dose is 600 mg		
H7N9 pediatric patients Children <5 years, with highest risk for those aged <2 years old	Higher-dose NAIs; optimal dose is uncertain	NAIs (for example, 10 days of treatment) optimal duration is uncertain	Centers for Disease Control and Prevention[92] Longer courses of treatment (for example, 10 days of treatment) should be considered for severely ill hospitalized H7N9 patients
Infected with NAI-resistant virus	Once daily 10 mg/kg	5 days	Japan Pediatric Society[98]

Abbreviation: NAI, neuraminidase inhibitor.

test results are positive.[105,106] Suspected flu cases[107] are mostly diagnosed with influenza within 48 hours after the onset of illness. Then, prompt treatment with NAIs is initiated. Unfortunately, the rapid diagnostic test sensitivity is low.[107]

In the US, over one-third of cases during the past two seasons received no antiviral treatment.[108] Lindegren and Schaffner[109] reported that several elements are necessary for earlier antiviral treatment, including more effective studies of antivirals on meaningful clinical endpoints among those at highest risk, and more sensitive and specific rapid diagnostic tests. Treatment within 48 hours of illness onset was significantly associated with survival (P=0.04). In cases where NAI treatment was initiated earlier in the course of the illness, these patients were less likely to die.[110] The recent decreased frequency of NAI treatment for influenza might be placing untreated critically ill children at an increased risk of death.[43] Early antiviral treatment in high-risk patients with influenza infection might significantly reduce secondary bacterial pneumonia, unnecessary antibiotic prescription, and health care-associated costs. Japan might have had the lowest case fatality rate (<0.001%; 198/20.7 million) in the H1N1 pandemic of 2009, mainly because of the universal implementation of early treatment with NAI.[111] The second main reason might be that early treatment was initiated for all patients nationwide using doctors' clinical judgment. A third reason might be that peramivir is not expensive in Japan because peramivir is a long-acting NAI, administered only on the first treatment day.[111] The Japanese example highlights possibilities for the reduction of influenza mortality in other countries.

Conclusion

Peramivir, which is generally safe and well tolerated, can be effective in adult and pediatric patients with influenza infection. In recent years, the potential threat of influenza pandemics and the constant emergence of new anti-influenza, drug-resistant influenza viruses have weakened the defensive role of the current anti-influenza drugs.

Antivirals, including peramivir, are still widely used in Japan after the pandemic. The clinical benefits of early antiviral treatment, the estimated cost effectiveness, and the effectiveness of antiviral drugs against mutant viruses must be acknowledged worldwide to minimize influenza-related mortality.

Disclosure

The authors report no conflicts of interest in this work.

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