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Kirk M Chan-Tack, Christine Kim, Alicia Moruf, Debra B Birnkrant

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Short communication

Clinical experience with intravenous zanamivir under an Emergency IND program in the United States (2011–2014)

Kirk M Chan-Tack[1], Christine Kim[1], Alicia Moruf[1], Debra B Birnkrant[1]*

[1]Division of Antiviral Products, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA

*Corresponding author e-mail: kirk.chan-tack@fda.hhs.gov

Abstract

Background: Since the emergence of 2009 H1N1 virus, IV zanamivir has been authorized as an investigational treatment for patients with serious and life-threatening influenza through an Emergency Investigational New Drug application (EIND). This review encompasses FDA's EIND database from May 2011-June 2014.

Methods: Retrospective descriptive review of patient clinical data in FDA's IV zanamivir EIND database from May 2011-June 2014.

Results: Of 364 IV zanamivir EIND requests, most patients (83%) were aged 18-64 years; 8 (2%) were pregnant, 29 (8%) were children. 234 patients (64%) had ≥1 co-morbidity reported. The majority (87%) were receiving oseltamivir when IV zanamivir was requested, and 33% had suspected (n=120; no improvement or worsening on oseltamivir) H275Y oseltamivir resistance. Influenza A was reported for 300 patients: confirmed 2009 H1N1 (n=163), suspected 2009 H1N1 (n=8), confirmed H3N2 (n=4), not subtyped (n=125). Influenza B was reported for 25 patients. Many patients (87%) required invasive mechanical ventilation, 23 (6%) received high frequency oscillatory ventilation, and 74 (20%) received extracorporeal membrane oxygenation (ECMO). 289 patients (79%) had ≥1 complication such as renal failure (n=124; 77/124 required dialysis), bacteremia (n=18), shock (n=95), or pneumonia (n=159). Of 134 patients (37%) with available outcome data, 83 died, and 51 survived.

Conclusions: IV zanamivir EIND authorizations were for treatment of critically ill adult patients with 2009 H1N1, including a substantial number with suspected oseltamivir resistance. Data from prospective, randomized controlled trials are needed and are ongoing to assess the safety and efficacy of IV zanamivir for treatment of hospitalized patients with severe influenza.

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Running Head: Intravenous zanamivir and Emergency IND

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Background

This report provides an updated summary of the available information on intravenous (IV) zanamivir from the Food and Drug Administration (FDA)'s Emergency Investigational New Drug application (EIND) process [1,2]. Since the emergence of 2009 H1N1 influenza A virus, IV zanamivir has been authorized as an investigational treatment for patients with serious and life-threatening influenza through an EIND application to the FDA. As part of the EIND process, treating physicians are encouraged to submit data to the FDA but reporting of requested data is voluntary.

Methods

We reviewed FDA's EIND database on influenza patients who received IV zanamivir from May 2011 through June 2014. Data was submitted by health care providers ("sponsors") who requested EINDs. For the 364 patients identified, we performed a descriptive analysis of reported patient information on age, gender, pregnancy status, baseline co-morbidities, virologic testing, antiviral resistance data, other antiviral treatments, clinical complications, supportive care modalities used, IV zanamivir treatment duration, adverse events (AEs), and outcomes (Tables 1 and 2).

Results

At the time of IV zanamivir request, many patients were critically ill with underlying co-morbidities and required intensive care unit admission for severe complications of influenza A (predominantly 2009 H1N1 virus), including respiratory failure and renal failure (Table 1). Of 364 IV zanamivir EIND requests, most patients (83%) were aged 18-64 years; 8 (2%) were pregnant, 29 (8%) were children. Two hundred and thirty four (64%) patients had ≥1 co-morbidity reported, including cancer (n=42), chronic lung disease (n=53), diabetes (n=66), obesity (n=49), chronic renal failure (n=15), heart disease (n=42), chronic liver disease (n=8), or HIV/AIDS (n=6). The majority (87%) of patients were receiving oseltamivir when IV zanamivir was requested. Although 33% of patients had clinically suspected oseltamivir resistance (defined as the treating physicians' clinical assessment that patients were experiencing either no improvement or were clinically worsening on oseltamivir), only one patient at the time of IV zanamivir request had confirmed oseltamivir resistance associated with the H275Y mutation in viral neuraminidase.

Influenza A was reported for 300 (82%) patients: confirmed 2009 H1N1 (n=163), suspected 2009 H1N1 (n=8), confirmed H3N2 (n=4), not subtyped (n=125). Influenza B was reported for 25 patients. At the time of IV zanamivir request, many patients (87%) required invasive mechanical ventilation, 23 (6%) received high frequency oscillatory ventilation, and 74 (20%) received extracorporeal membrane oxygenation (ECMO). Two hundred and eighty nine (79%) patients reported ≥1 complication at the time of IV zanamivir request, such as renal failure (n=124; 77 of these 124 patients required dialysis), bacteremia

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(n=18), shock (n=95), or pneumonia (n=159). Other publications of 2009 H1N1 patients have reported fewer complications at the time of IV zanamivir initiation [3–6].

Of 134 (37%) patients with available outcome data, 83 died, and 51 survived. Of 53 patients (14.5%) with AE data, 31 reported no AEs during IV zanamivir treatment, and 23 reported AEs during IV zanamivir treatment (Table 2). Two or more subjects reported the following AEs during IV zanamivir treatment: increasing liver function tests (n=7); rash (n=3); renal failure (n=3); multi-organ failure (n=2). However, the presence of multiple confounders and limitations of the available data precluded any definitive causality assessments that might suggest a possible relationship to IV zanamivir.

Discussion

Given the unmet medical needs for hospitalized patients with serious, life-threatening influenza and the number of EIND requests, our findings suggest the public health importance of developing an intravenous anti-influenza agent for use in this patient population.

This report also highlights some general limitations of EINDs. Inadequate reporting of clinical outcomes and adverse events in the EIND database prevented detailed analysis of either parameter. As part of the EIND process, health care providers (“sponsors”) who request EINDs are encouraged to submit data to the FDA. Despite numerous requests for sponsors to submit follow-up data after an EIND is authorized, reasons for this small fraction of follow-up reports are unclear. After an EIND is authorized, it is possible clinicians may not feel inclined to dedicate the necessary resources to submit follow-up reports because they may view an EIND more as treatment access rather than an actual investigational single-patient protocol. Despite multiple requests over a prolonged time-period to health care providers (“sponsors”) who requested EINDs, the summarized data represents the cumulative data, though limited, received for these patients (Tables 1 and 2).

Our findings have some important limitations. First, limited microbiologic data was available; only 20 out of 159 patients with pneumonia reported microbiologic data; 8 out of 18 patients with bacteremia had microbiologic data documented. Second, limited outcome, follow-up, or adverse event (AE) data were reported. Third, interpretation of data is limited by the retrospective and uncontrolled design to assess differences in data reported (e.g. clinical outcomes, microbiologic data, diagnostic data, AEs).

Most IV zanamivir EIND authorizations were for late treatment of critically ill adult patients with 2009 H1N1 influenza A, including a substantial number with clinically suspected oseltamivir resistance. However, conclusions regarding the clinical effectiveness or safety of IV zanamivir for treatment of critically ill influenza patients cannot be derived from these data. Data from prospective, randomized controlled trials are needed and are ongoing to assess the safety and efficacy of IV zanamivir for treatment of hospitalized patients with severe influenza [7].

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Acknowledgment statement

This work does not represent the viewpoint of the FDA and does not constitute FDA regulatory guidance. Comments and conclusions discussed in this article are not binding on the public or the FDA. Patients described in this review received intravenous zanamivir from GlaxoSmithKline.

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A.M. contributed to the data analysis and approved the final manuscript as submitted. D.B.B. contributed to the study concept, critically reviewed and contributed to revising the manuscript, and approved the final manuscript as submitted.

References

1. Chan-Tack K, Gao A, Himaya A, *et al*. Clinical Experience with Intravenous Zanamivir for Influenza Treatment under an Emergency IND program in the United States. *J Infect Dis* 2013; **207:**196–198.

2. “Emergency use of an investigational new drug (IND).” Title 21 Code of Federal Regulations, Part 312.36. 2009 ed., 66.

3. Fraaij PL, van der Vries E, Beersma MF, *et al*. Evaluation of the antiviral response to zanamivir administered intravenously for treatment of critically ill patients with pandemic influenza A (H1N1) infection. *J Infect Dis* 2011; **204:**777–782.

4. Wijaya L, Chua YY, Cui L, *et al*. Intravenous zanamivir in critically ill patients due to pandemic 2009 H1N1 influenza A virus. *Singapore Med J* 2011; **52:**481–485.

5. Harter G, Zimmermann O, Maier L, *et al*. Intravenous zanamivir for patients with pneumonitis due to pandemic (H1N1) 2009 influenza virus. *Clin Infect Dis* 2010; **50:**1249–1251.

6. Marty FM, Man CY, van de Horst C, *et al*. Safety and pharmacokinetics of intravenous zanamivir treatment in hospitalized adults with influenza: an open-label, multicenter, single-arm, phase II study. *J Infect Dis* 2014; **209:**542–550.

7. www.clinicaltrials.gov. A study of intravenous zanamivir versus oral oseltamivir in adults and adolescents hospitalized with influenza. Accessed February 5, 2015.

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Table 1. Clinical characteristics reported at the time of the EIND request in 364 patients for whom intravenous zanamivir was requested via EIND (May 2011-June 2014)

Parameter	Total (%)[a]
Age	
Median	45 years
Mean	45 years
Range	8 days to 103 years
Sex	
Male	219 (60.2)
Female	141 (38.7)
Pregnant	8 (2.2)
Not Reported	4 (1.1)
Race/Ethnicity	Not reported
Baseline co-morbidities[b]	
Cancer	42 (11.5)
Chronic lung disease	53 (14.65)
Obesity	49 (13.5)
Diabetes	66 (18.1)
Chronic renal failure	15 (4.1)
Hypertension	71 (19.5)
Heart disease	42 (11.5)
HIV/AIDS	6 (1.6)
Chronic liver disease	8 (2.2)
Immunosuppression[c] (not cancer, not HIV/AIDS)	20 (5.5)
None (i.e. medical record stated patient had no baseline co-morbidities)	81 (22.2)
Not reported	49 (13.5)
Time of onset of illness at the time of IV zanamivir request	
1 – 2 days	27 (7.4)
3 – 4 days	42 (11.5)
5 – 10 days	116 (31.9)
≥10 days	78 (21.4)
Not reported	101 (27.7)
Baseline influenza testing data	
Influenza A	300 (82.4)
2009 H1N1 – confirmed	163 (44.7)
2009 H1N1 – suspected	8 (2.2)
H3N2 – confirmed	4 (1.1)
Subtype not reported	125 (34.3)
Influenza B	25 (6.9)
Subtype not reported	24 (6.6)
Influenza type not specified	24 (6.6)
Influenza type not reported (i.e. no information was available)	11 (3)
Influenza testing negative	4 (1.1)
Baseline virologic resistance data	
Not reported	142 (39)

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Not suspected by clinician	101 (27.7)
H275Y oseltamivir resistance – laboratory confirmed[d]	1 (0.3)
H275Y oseltamivir resistance – suspected by clinical assessment[e]	120 (33)
Other antivirals used prior to or at the time of EIND request	
Oseltamivir	315 (86.5)
Peramivir[f]	0 (0)
Inhaled Zanamivir	1 (0.3)
Amantadine[g]	3 (0.8)
Rimantadine[h]	2 (0.6)
Ribavirin	0 (0)
Not reported	26 (7.1)
No neuraminidase inhibitor treatment was used	22 (6)
Complications reported at the time of EIND request	
Pneumonia[i]	159 (43.7)
Lobar infiltrate	7 (1.9)
Bilateral infiltrate	48 (13.1)
Details/description of infiltrate were not provided	104 (28.6)
Acute renal failure	124 (34.1)
Shock and/or multi-organ failure	95 (26.1)
Bacteremia[j]	18 (4.9)
Supportive care reported at the time of EIND request	
Intubation/invasive mechanical ventilation	317 (87.1)
Dialysis	77 (21.1)
Extracorporeal membrane oxygenation	74 (20.3)
Oscillating ventilator	23 (6.3)
BiPAP	8 (2.2)
No supportive care required	16 (4.4)
Not reported	14 (3.8)
IV zanamivir treatment duration	
Not reported	333 (91.5)
≤5 days of treatment	16 (4.4)
>5 days of treatment	15 (4.1)

[a]Percentages may not equal 100% due to rounding.
[b]Some individuals had more than one baseline comorbidity.
MSSA, methicillin-sensitive Staphylococcus aureus; MRSA, methicillin-resistant Staphylococcus aureus; GAS, Group A Streptococcus; GBS, Group B Streptococcus; spp, species.
[c]Stem cell transplant (n=9); Renal transplant (n=5); Graft versus host disease (n= 3); Lung transplant (n=3); Chronic steroid use (n=2).
[d]Confirmed oseltamivir resistance was defined as laboratory confirmation of the H275Y mutation in viral neuraminidase from patient specimen(s).
[e]Clinically suspected oseltamivir resistance was defined as the treating physicians' clinical assessment that patients were experiencing either no improvement or were clinically worsening despite receiving oseltamivir. Of 120 patients in this subgroup, 27 patients had specific baseline co-morbidities that were documented by the treating physicians as contributing to their concern for the potential of oseltamivir resistance. These baseline co-morbidities were: Cancer (n=16); Stem cell transplant (n=5); Graft versus host disease (n= 3); Chronic steroid use (n=2); Lung transplant (n=1). No virology data was available for these patients to document whether laboratory confirmed oseltamivir resistance was detected.
[f]During the period covered by this database review, IV peramivir was not available via EIND.

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[g]Of 3 patients who received oral amantadine, 1 patient also received rimantadine (note: amantadine and rimantadine were not given concurrently in this patient); the other 2 patients received oral amantadine only.
[h]Of 2 patients who received oral rimantadine, 1 patient also received amantadine (note: amantadine and rimantadine were not given concurrently in this patient); the other patient received oral rimantadine only.
[i]Microbiologic data reported for cases of pneumonia: MSSA (n=6); MRSA (n=4); Streptococcus pneumoniae (n=2); Pseudomonas aeruginosa (n=2); Legionella pneumophila (n=1); GAS (n=1); GBS (n=1); Klebsiella pneumoniae (n=1); Aspergillus spp. (n=2).
[j]Microbiologic data reported for cases of bacteremia: S. pneumoniae (n=5); GAS (n=1); P. aeruginosa (n=1); Escherichia coli (n=1); [There was also one reported case of fungemia with Candida albicans].

Table 2. Follow-up data

Parameter	**Total (%)[a]**
Outcome/follow-up data	
Number of patients with available outcome data	134
Died	83 (61.9)
Survived	51 (38.1)
Reported clinical improvement	40 (29.9)
Reported no clinical improvement	11 (8.2)
Adverse Events (AE)	
Number of patients with available AE data	53
No AEs occurred	31 (58.4)
AEs occurred[b]	22 (41.5)

[a]Percentages may not equal 100% due to rounding.
[b]Two or more subjects reported the following AEs: Increasing liver function tests (n=7); Rash (n=3); Renal failure (n=3); Multi-organ failure (n=2).