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Clinical Experience With Intravenous Zanamivir Under an Emergency Investigational New Drug Program in the United States

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To the Editor—We read the article by Fraaij et al [1] and would like to summarize the available information on intravenous zanamivir from the Food and Drug Administration (FDA)'s Emergency Investigational New Drug (EIND) application process [2]. No intravenous antiviral agents for treatment of severe influenza are currently approved in the United States. Since the emergence of 2009 pandemic influenza A virus subtype H1N1 (A[H1N1]pdm09), intravenous zanamivir has been authorized through an EIND application to the FDA as an investigational treatment for patients with serious and life-threatening influenza. As part of the EIND process, treating physicians are encouraged to submit data to the FDA, but reporting of requested data is voluntary. We reviewed the FDA's EIND database on influenza patients who received intravenous zanamivir from April 2009 through April 2011. For the 200 patients identified, we performed a descriptive analysis of reported patient information on age, sex, pregnancy status, baseline comorbidities, virologic test results, antiviral resistance data, other antiviral treatments, clinical complications, supportive care modalities used, intravenous zanamivir treatment duration, adverse events (AEs), and outcomes (Table 1).

At the time of intravenous zanamivir request, many patients were critically ill with underlying comorbidities and required intensive care unit admission for severe complications of influenza A virus infection (predominantly due to A[H1N1]pdm09), including respiratory failure and renal failure. Most patients (78.5%) had received prior or concomitant antiviral agents, mainly oseltamivir, although some (10%) had also received intravenous peramivir. Nine percent of patients (mostly with comorbidities and/or immunosuppression) had documented oseltamivir resistance associated with the H275Y

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mutation in viral neuraminidase, and overall approximately 25% of intravenous zanamivir requests were for patients with confirmed or clinically suspected oseltamivir resistance. Other published case series of A(H1N1) pdm09-infected patients have reported fewer complications at the time of intravenous zanamivir initiation and fewer reports of oseltamivir resistance [1, 3-7].

Our findings have several important limitations. First, almost no microbiologic data were provided in cases in which patient narratives reported pneumonia or bacterial coinfection. In 69 of 73 cases reporting pneumonia, microbiologic or additional clinical data were not available to determine whether cases of pneumonia represented secondary bacterial infection or primary influenza virus pneumonitis. In 4 pneumonia cases, methicillin-resistant *Staphylococcus aureus* (MRSA) infection (in 3 cases) or *Pneumocystis jirovecii* infection (in 1 case) was reported. In 15 of 19 cases reporting bacterial coinfection, microbiologic or additional clinical data were not provided to delineate the source (eg, blood, urine, skin, central nervous system, or catheter related), etiology, or severity of the bacterial infection. Four cases had microbiologic or clinical information in which MRSA bacteremia (in 3 cases) or *Streptococcus pyogenes* skin and soft-tissue infection (in 1 case with concomitant burns) was reported. Second, limited outcome, follow-up, or adverse event data were reported. Third, interpretation of data is limited by the retrospective and uncontrolled design to assess differences in data reported (eg, clinical outcomes, microbiologic data, diagnostic data, and adverse events).

Most intravenous zanamivir EIND authorizations were for late treatment of critically ill adult patients with A(H1N1) pdm09 infection, including a subset with confirmed or suspected oseltamivir resistance. It is possible that cases of oseltamivir resistance could increase in the future [8, 9]. However, conclusions regarding the clinical effectiveness or safety of intravenous zanamivir for treatment of critically ill influenza patients cannot be drawn from these data; randomized clinical trials are needed and are ongoing [10].

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Table 1.

Clinical Characteristics of 200 Patients for Whom Intravenous (IV) Zanamivir Was Requested via an Emergency Investigational New Drug (EIND) Program, April 2009–April 2011

Parameter	Value
EIND requests, by interval	
April–July 2009	0
August 2009–July 2010	99 (49.5)
August 2010–April 2011	101 (50.5)
Age, y	
Median (range)	47 (0.5–91)
Mean	47
0–4	15 (7.5)
5–9	9 (4.5)
10–17	15 (7.5)
18–49	96 (48)
50–64	54 (27)
≥65	11 (5.5)
Sex	
Male	95 (47.5)
Female	105 (52.5)
Pregnant	14 (7)
Race/ethnicity	Not reported
Baseline comorbidity	
Cancer	36 (18)
Chronic lung disease	26 (13)
Obesity	17 (8.5)
Diabetes	9 (4.5)
Chronic renal failure	8 (4)
Heart disease	7 (3.5)
HIV/AIDS	2 (1)
Cirrhosis	1 (0.5)

Parameter	Value
Immunosuppression[a] (not cancer, not HIV/AIDS)	17 (8.5)
Not reported	97 (48.5)
Baseline influenza virus detected	
Influenza A virus	177 (88.5)
Any	
A(H1N1)pdm09	
Confirmed	98 (49)
Suspected	18 (9)
Subtype H3N2, confirmed	1 (0.5)
Subtype not reported	60 (30)
Influenza B virus	12 (6)
Virus type not reported	11 (5.5)
Baseline virologic resistance data	
Not reported	149 (74.5)
H275Y oseltamivir resistance	
Confirmed[b]	18 (9)
Immunosuppressed patients[c]	11 (5.5)
Suspected[b]	33 (16.5)
Immunosuppressed patients[d]	12 (6)
Antivirals used prior to or at time of EIND request	157 (78.5)
Oseltamivir	152 (76)
Peramivir[e]	20 (10)
Inhaled zanamivir[f]	8 (4)
Amantadine[g]	3 (1.5)
Rimantadine[h]	3 (1.5)
Ribavirin[h]	3 (1.5)
Not reported	43 (21.5)
Complications reported at time of EIND request	

Parameter	Value
Pneumonia[i]	73 (36.5)
Lobar infiltrate	57 (28.5)
Bilateral infiltrate	16 (8)
Acute renal failure	50 (25)
Shock and/or multiorgan failure	25 (12.5)
Bacterial infection[i]	19 (9.5)
Supportive care reported at time of EIND request	
Intubation/invasive mechanical ventilation	134 (67)
Dialysis	38 (19)
Extracorporeal membrane oxygenation	27 (13.5)
Oscillating ventilator	16 (8)
IV zanamivir treatment duration	
Not reported	160 (80)
≤5 d	22 (11)
>5 d	18 (9)
Outcome/follow-up data	
Not reported	153 (76.5)
Died	21 (10.5)
Survived	26 (13)
Clinical improvement	18 (9)
No clinical improvement	8 (4)

Data are no. (%) of patients, unless otherwise indicated.

Abbreviation: HIV, human immunodeficiency virus.

[a]Renal transplantation (n = 6), lung transplantation (n = 3), congenital immunodeficiency (n = 4), chronic use of steroids (n = 2), and rheumatoid arthritis with chronic use of tumor necrosis factor blocker (n = 2).

[b]All had received oseltamivir.

[c]Cancer (n = 8), renal transplantation (n = 1), lung transplantation (n = 1), and congenital immunodeficiency (n = 1).

[d]Cancer (n = 8), renal transplantation (n = 2), chronic use of steroids (n = 1), and rheumatoid arthritis with chronic use of tumor necrosis factor blocker (n = 1).

[e]Eighteen also previously received oseltamivir, and 2 received IV peramivir only.

[f] Five also received oseltamivir, and 3 patients received inhaled zanamivir only.

[g] One also received oseltamivir, 1 also received IV peramivir, and 1 received oral amantadine only.

[h] All also received oseltamivir.

[i] Few EIND narratives reported microbiologic data.