Intravenous Zanamivir in Hospitalized Patients With Influenza

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abstract

BACKGROUND: Children with severe influenza infection may require parenteral therapy if oral or inhaled therapies are ineffective or cannot be administered. Results from a study investigating intravenous (IV) zanamivir for the treatment of hospitalized infants and children with influenza are presented.

METHODS: This phase II, open-label, multicenter, single-arm study assessed the safety of investigational IV zanamivir in hospitalized children with influenza. Safety outcomes included treatment-emergent adverse events (TEAEs), clinical laboratory measurements, and vital signs. Clinical outcomes, pharmacokinetics, and virologic efficacy data were collected as key secondary outcomes.

RESULTS: In total, 71 children received treatment with investigational IV zanamivir (exposure comparable to 600 mg twice daily in adults). TEAEs and serious TEAEs (STEAEs) were reported in 51 (72%) and 15 (21%) patients, respectively. The mortality rate was 7%, and median durations of hospital and ICU stays were 6 and 7.5 days, respectively. No STEAEs or deaths were considered related to IV zanamivir treatment, and no patterns of TEAEs, laboratory abnormalities, or vital signs were observed. The mean zanamivir exposures from 34 patients with normal renal function who received 12 mg/kg, 14 mg/kg, or 600 mg of IV zanamivir ranged from 64.5 to 110 hour·μg/mL. The median change from baseline in the viral load was −1.81 $\log_{10}$ copies per mL after 2 days of treatment.

CONCLUSIONS: The safety profile of IV zanamivir was favorable, with no drug-related STEAEs reported. The majority of children experienced virologic response and clinical improvement during the treatment course. Systemic zanamivir exposures in children were consistent with adults.

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Drs Blumer and Romero participated as study investigators, enrolling patients into the trial, interpreting the data, and preparing the manuscript; Drs Bradley, Kimberlin, Michaels, Yamamoto, and Pahud were the site's principal investigators, enrolled children into the trial, assisted in the review and analysis of data, and assisted in the drafting and revising of the manuscript; Ms Roberts conducted the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript; Dr Hossain was involved in the initial pharmacokinetic analyses and

WHAT'S KNOWN ON THIS SUBJECT: A phase II, open-label study of intravenous (IV) zanamivir in hospitalized adults has been previously published. Safety and pharmacokinetic and clinical results from this study supported further investigation of the use of IV zanamivir.

WHAT THIS STUDY ADDS: The adjusted dose of IV zanamivir provided comparable exposures in children to those seen in adults, and the majority of treated children experienced clinical improvement with a favorable safety profile.

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Influenza pandemics and seasonal influenza epidemics cause substantial global morbidity and mortality.[1] Treatment options remain limited, and the emergence of resistance to anti-influenza drugs threatens to further limit available treatment options.[2]

Groups at risk for severe and even fatal influenza infections have been identified over the past decade. These include children <2 years of age (who experience increased rates of serious illness and death), term and preterm infants <6 months of age (who cannot receive influenza vaccination because of their age), and children ≥6 months of age with conditions that increase the risk of complications from influenza (such as asthma, diabetes, cardiac disease, immunosuppression, obesity, or neurologic and neurodevelopmental disorders).[3]

Zanamivir is a neuraminidase (NA) inhibitor approved in the United States as an oral inhalation powder for the treatment of acute (symptomatic <2 days), uncomplicated influenza in children ≥7 years of age and prophylaxis in children ≥5 years of age.[4,5] In some circumstances, the intravenous (IV) administration of zanamivir may be the most appropriate formulation for hospitalized infants and children, such as for patients who are unable to tolerate oral administration of other NA inhibitors, when tolerability of an inhalation agent is an issue, or when antiviral resistance is a concern. Zanamivir retains activity against influenza viruses harboring the most common resistance substitution, H275Y, which confers high-level resistance to oseltamivir and reduced susceptibility to peramivir in N1 viruses.[6]

A phase II, open-label study of IV zanamivir (600 mg twice daily) in hospitalized adults provided safety, pharmacokinetic (PK), and clinical outcomes data that supported further investigation of the use of IV zanamivir.[7] Authors of a phase III study demonstrated that IV zanamivir had similar efficacy and safety to oral oseltamivir in hospitalized adults and adolescents with influenza.[8] However, experience with IV zanamivir in the pediatric population is limited.

Results of a phase II open-label study evaluating the safety, clinical, PK, and virologic outcomes of IV zanamivir for the treatment of influenza in hospitalized pediatric patients are presented.

METHODS

Study Design

This was an open-label, multicenter, single-arm study to assess the safety of investigational IV zanamivir in hospitalized pediatric patients with severe influenza. Clinical, PK, and virologic data were assessed as key secondary outcomes (Clinical Trials registration: NCT01014988; GlaxoSmithKline identifier: NAI113678). The study was performed in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice and the principles of the Declaration of Helsinki and was approved by local ethics committees. Informed consent was obtained from the parent or legal guardian (and the patient when assent was appropriate) before any study procedures were undertaken.

Key enrollment criteria included patients ≥6 months and <18 years of age who were hospitalized with local laboratory-confirmed severe or progressive symptomatic influenza while receiving approved antiviral agents (or who were deemed unsuitable for treatment with such agents) and for whom parenteral NA inhibitor therapy was considered the most appropriate. Full enrollment criteria and exclusion criteria are presented in Supplemental Information.

Treatment

Patients received an age-adjusted, weight-based IV dose of zanamivir, calculated to provide comparable systemic exposure to 600 mg twice daily in adults. Doses were administered twice daily at a constant rate infusion over 30 minutes. Full details, including dose adjustment based on the patient's renal function, can be found in Supplemental Table 4 and Supplemental Information. Patients received IV zanamivir for 5 days and up to 10 days if viral shedding was ongoing or clinical symptoms warranted further treatment (at the discretion of the local investigator). The study duration was 28 days for patients whose treatment duration was 5 days and up to 33 days for those whose treatment duration was extended to a maximum of 10 days.

Outcome Measures

Primary Outcome Measure: Safety

Primary safety outcomes included the following: treatment-emergent adverse events (TEAEs) (per the Division of AIDs toxicity scale)[9]; serious TEAEs (STEAEs); the monitoring of abnormal clinical laboratory measurements (including incidents of hepatic injury: liver event TEAEs defined as alanine transaminase [ALT] ≥5 × upper limit of normal [ULN]; STEAEs defined as per Hy's law criteria [ALT ≥3 × ULN and total bilirubin ≥2 × ULN]); electrocardiograms; and vital signs. TEAEs were considered drug-related events if deemed by the local study investigator to be possibly related to the study drug on the basis of their time course relative to drug exposure and an adverse outcome worse or different than that expected for the underlying illness.

Secondary Outcome Measures

Clinical endpoints included the incidence of and time to a positive clinical response (a composite endpoint defined as the resolution of at least 4 of 5 vital signs for at least 24 hours [afebrile status, oxygen saturation, respiratory status, heart rate, and systolic blood pressure] or hospital discharge); length of hospitalization (measured from study day 1); total duration of ICU stay; the proportion of patients requiring mechanical ventilation; and mortality rate at day 14 and day 28. Full details are presented in Supplemental Information and Supplemental Table 5. For the purpose of this study, vital signs were recorded only once daily. As a result, the time to clinical response (TTCR) was often determined by hospital discharge; however, if vital sign resolution was documented and confirmed at 24 hours, that would also meet the clinical response criteria. PK analysis was performed after initial and maintenance dosing. Serum PK assessments were performed wherever possible but were only mandatory for patients in the 6 month to <1 year age cohort. PK parameters for patients on extracorporeal membrane oxygenation (ECMO), continuous renal replacement therapies, or both were analyzed separately.

Nasopharyngeal (NP) swabs were collected for virologic outcomes and were analyzed by Q^2 (formerly Quest Diagnostics, Madison, NJ) and Viroclinics Biosciences (Rotterdam, Netherlands). A limited number of throat swabs and endotracheal (ET) samples were also collected for analysis. Change in influenza viral load over time and time to virologic improvement (determined by quantitative real-time polymerase chain reaction [qRT-PCR] and defined as a 2-log reduction in viral load or undetectable viral RNA) were assessed by using NP samples. Influenza subtyping was conducted, and the influenza genotype and phenotype were assessed (full methods are presented in Supplemental Information).

Study Procedures

Safety and clinical outcomes were assessed daily during treatment and after treatment on days 2, 5, 9, 16, and 23 (after the last dose of IV zanamivir). PK samples were collected before infusion; at the end of infusion; and 1 to 2, 4 to 6, and 11 to 12 hours after the start of infusion on Day 1 and on Day 3, 4, or 5 if the dose was adjusted for renal function. If the start of maintenance dosing was delayed because of renal impairment, then additional samples were scheduled for 22 to 24 and 46 to 48 hours postinfusion. NP swabs were performed on days 1, 3, and 5 of treatment, and if patients were symptomatic and remained hospitalized, additional samples were taken on days 7 and 10 of treatment and days 2, 5, 9, 16, and 23 after the last dose of IV zanamivir.

Statistical Analysis

There was no formal sample size calculation for this study; the sample size was chosen on the basis of feasibility concerns and to provide a suitable number of patients to assess the safety of IV zanamivir in pediatric patients. Further information on target recruitment can be found in the Supplemental Information.

Safety and clinical endpoints are presented descriptively, without formal statistical comparisons. PK parameters were analyzed using conventional noncompartmental methods and Phoenix WinNonlin. A post hoc analysis of the relationship between the day 3 viral load change from baseline and TTCR was investigated by using Pearson's correlation analysis. Both the intent-to-treat exposed (ITT-E) and safety population consisted of all patients who received ≥1 dose of IV zanamivir and were used for all analyses.

RESULTS

Study Population

In total, 73 children were enrolled from 25 centers in 5 countries during 3 Northern Hemisphere and 3 Southern Hemisphere influenza seasons between September 16, 2010, and February 13, 2015. Two patients withdrew consent before receiving the study drug; 71 patients received ≥1 dose of zanamivir (Supplemental Fig 3). Overall, 66% were boys, the median age was 7 years (range: 0.6–17 years), and 56% had ≥1 chronic underlying medical condition (Table 1). The most common influenza symptoms at baseline were fever (89%), cough (75%), nasal symptoms (49%), and dyspnea (48%). The median time from onset of symptoms to initiation of investigational IV zanamivir was 4 days (range: 0–7 days). At study entry, 24 (34%) patients were on mechanical ventilation and an additional 4 (6%) patients were on ECMO. Eight (11%) patients had received an influenza vaccine in the 9 months before the study, and 49 (69%) patients had received oseltamivir before study entry, with a median duration of treatment of 2 days (range: 1–11 days). Patients who received a single dose on day 1 would have received their last dose on day 6 for the standard course of 10 doses over 5 days. In total, 57 patients received IV zanamivir for ≤5 days (median: 5 days; range: 1–6). At the discretion of the investigator, 14 patients received IV zanamivir for >5 days (median: 11 days; range: 6–11).

Safety Endpoints

Overall, TEAEs, grade 3 or 4 TEAEs, and STEAEs were reported in 51 (72%), 23 (32%), and 15 (21%) patients, respectively. Summaries of grade 3 or 4 TEAEs and STEAEs are presented in Tables 2 and 3. A summary of all TEAEs is presented in Supplemental Table 6. STEAEs were reported less frequently in younger

TABLE 1 Summary of Baseline Characteristics, Demographics, and Chronic Underlying Illnesses

Characteristic ($N = 71$)	Baseline Value
Age cohort, *n*	
Cohort 1: 6 mo–<1 y	7
Cohort 2: 1–<2 y	11
Cohort 3: 2–<6 y	12
Cohort 4: 6–<13 y	27
Cohort 5: 13–<18 y	14
Age in years, median (minimum, maximum) [*n*]	7.0 (0.6, 17) [71]
Sex, *n* (%)	
Male	47 (66)
Race, *n* (%)	
African American or African	13 (18)
Japanese	3 (4)
Native Hawaiian or Pacific Islander	1 (1)
White (Arabic or North African)	2 (3)
White (Caucasian or European)	48 (68)
Multiracial	3 (4)
Unknown	1 (1)
Chronic underlying illnesses occurring in >2 patients, *n* (%)[a]	
Any illness	40 (56)
Asthma	21 (30)
Seizure disorder	8 (11)
Current cancer or cancer treatment within 1 y	6 (8)
Chronic lung disease	5 (7)
Malnutrition	4 (6)
Congenital heart disease	3 (4)
Symptoms of influenza, *n* (%)	
Fever	63 (89)
Cough	53 (75)
Nasal symptoms (rhinorrhea, congestion)	35 (49)
Dyspnea	34 (48)
Fatigue and/or malaise	32 (45)
Vomiting	28 (39)
Anorexia	22 (31)
Headache	16 (23)
Myalgia	16 (23)
Sore throat	15 (21)
Nausea	14 (20)
Diarrhea	13 (18)
Respiratory status, *n* (%)[b]	
Machine-assisted, noninvasive: CPAP	2 (3)
Machine-assisted, noninvasive: BiPAP	3 (4)
Machine-assisted: ECMO	4 (6)
Machine-assisted: ET mechanical ventilation	24 (34)
Supplemental oxygen delivery[b]	
Face mask	4 (6)
Nasal cannula	6 (8)
Face tent	0
High flow	2 (3)

BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure.

[a] Some patients were documented to have multiple chronic underlying illnesses.

[b] Patients who received oxygen delivery listed under "Supplemental oxygen delivery" are exclusive of those who received mechanical ventilation listed under "Respiratory status."

children (<6 years of age) relative to older children and adolescents (Table 3). No STEAE was considered related to the study treatment by the study investigator. Five (7%) patients died during the study (encephalitis, respiratory failure, multiorgan failure, lactic acidosis, and brain herniation), 3 (4%) of whom were on therapy. No deaths were considered related to IV zanamivir by the study investigator. The cause of death was considered influenza-related for 3 patients. Two patients who died had chronic underlying conditions (asthma, cancer).

The only TEAE that occurred in >1 patient and, in the opinion of the study investigator, was potentially attributable to the drug was neutropenia ($n = 2$, 3%; Table 3). No patterns of TEAEs, laboratory abnormalities, or unfavorable trends in vital signs were observed.

Clinical Endpoints

Overall, 65 (92%) patients treated with IV zanamivir experienced a positive clinical response as determined by the composite endpoint. Median TTCR was 6 days (range: 1–42 days); median duration of hospitalization was also 6 days (range: 1–45 days). Forty-six (65%) patients stayed in the ICU at some time during the study, with a median duration of 7.5 days (range: 2–50 days); this could have included days in the ICU before entry into the study. The number of patients receiving ECMO and mechanical ventilation decreased from 28 out of 71 (39%) at baseline to 17 out of 71 (24%) by day 5 and 3 out of 65 (5%) by the end of the study (posttreatment + 23 days; 6 patients did not complete to this stage because of death [$n = 5$] or from being lost to follow-up [$n = 1$]). Two of the 3 patients on mechanical ventilation at the end of study had been discharged previously but were subsequently readmitted to the hospital for non–influenza-related conditions (tachycardia and respiratory syncytial virus).

Serum PKs

A total of 53 (75%) patients had samples obtained for PK analysis and were included in the PK population. The baseline demographics and characteristics for this population were similar to the ITT-E population. The primary PK parameters for initial and maintenance dosing are summarized in Supplemental Tables 7 and 8. Overall, the PK parameters were similar in the pediatric cohort to those previously published for adults[7] (Supplemental Fig 4, post

TABLE 2 Summary of Any Grade 3 or 4 TEAEs Occurring in >1 Patient (Safety Population)

Adverse Event	*n* (%)
Any grade 3–4 event by age cohort	23 (32)
Cohort 1: 6 mo–<1 y (*N* = 7)	2 (29)
Cohort 2: 1–<2 y (*N* = 11)	5 (45)
Cohort 3: 2–<6 y (*N* = 12)	2 (17)
Cohort 4: 6–<13 y (*N* = 27)	10 (37)
Cohort 5: 13– <18 y (*N* = 14)	4 (29)
Any grade 3–4 event (*N* = 71)	23 (32)
Hypotension	3 (4)
Neutropenia	3 (4)
Respiratory failure	3 (4)
Anemia	2 (3)
Deep vein thrombosis	2 (3)
Drug withdrawal syndrome	2 (3)
Hyperbilirubinemia	2 (3)
Hypertension	2 (3)
Multiorgan failure	2 (3)
Pneumonia	2 (3)
Renal failure	2 (3)
Respiratory distress	2 (3)
Tachycardia	2 (3)

hoc analysis). The mean zanamivir exposure in 34 patients with normal renal function who received 12 mg/kg, 14 mg/kg, or 600 mg IV zanamivir ranged from 64.5 to 110 hour·μg/mL, which was generally consistent with that seen in adults (82.9–90.3 hour·μg/mL).[7] PK results from patients who received continuous renal replacement therapies and/or ECMO appeared similar to results from patients not receiving these procedures (Fig 1).

Virology

All 71 patients in the ITT-E population were identified as influenza-positive by local tests at the investigator sites. For confirmatory testing by the central laboratory, 70 patients provided NP samples, some also provided throat (*n* = 2) or ET (*n* = 6) samples, and 1 provided only ET samples. In total, 57 (80%) patients were confirmed influenza-positive by a polymerase chain reaction (PCR) assay. Twenty-five (35%) patients were positive for influenza subtype H3N2, 12 (17%) patients for H1N1pdm09, 19 (27%) patients for influenza type B, and 1 (1%) patient was coinfected with both A/H3N2 and B. The remaining 14 (20%) patients were identified as influenza-positive at investigator sites but were not confirmed at the central laboratory; this could be due to virus clearance by the time of study enrollment or false-positives from rapid antigen tests. For patients who were PCR positive at baseline (*n* = 55, 77%), the median baseline viral load was 6.66 $\log_{10}$ copies per mL, and the median viral load change from baseline was −1.81 $\log_{10}$ copies per mL after 2 days of treatment (day 3) and −2.94 $\log_{10}$ copies per mL after 4 days of treatment (Fig 2). No clear differences were observed in the median change from baseline in the viral load during the first week of treatment between patients who received antiviral agents before enrollment and antiviral-naïve patients (Supplemental Fig 5) and between patients treated for >5 days and ≤5 days (Supplemental Fig 6).

Median time to virologic improvement for the overall population was 3 days (range: 1–25 days). There was little difference in median time to virologic improvement among the age cohorts (range: 3–4 days). Among patients with a positive qRT-PCR at baseline, median time to virologic improvement was 4 days, again with little difference among the age cohorts. Eighteen patients received oseltamivir after the IV zanamivir treatment had been discontinued, 2 of whom also had post-IV zanamivir treatment virology assessments. Neither case impacted the time to virologic improvement endpoint; 1 patient achieved virologic improvement before discontinuing zanamivir, whereas the other never achieved virologic improvement and was therefore not included in the analysis. One patient received oseltamivir during treatment (protocol deviation) and achieved undetectable viral load while on treatment.

In a post hoc analysis, we investigated the relationship between viral load change from baseline at day 3 and TTCR. Among patients who were PCR positive at baseline, greater viral load decreases by day 3 were weakly associated with shorter TTCRs (Pearson's correlation coefficient = 0.2909; *P* = .065). This analysis did not take into account that a low baseline viral load would limit the magnitude of a day 3 viral load change.

None of the 10 patients with day 1 and post-day 1 virologic samples assayed developed phenotypic reduced susceptibility to zanamivir. One patient harbored a treatment-emergent resistance amino-acid substitution in the NA region (H1N1pdm09, E119G)[10] on day 5 that was not present at baseline, day 3, or day 7. No phenotypic data were available because the virus could not be cultured. This 9-month-old patient had received 3 days of oseltamivir before enrollment and 8 days of IV zanamivir after enrollment, and a day 1 area under the concentration-time curve (AUC) indicated appropriate exposure. Viral loads (qRT-PCR) were elevated through day 5, declined on day 7, and were undetectable on day 9 when the patient was discharged from the hospital. This patient had no underlying chronic illnesses and reported no STEAEs. Two

TABLE 3 Summary of All Drug-Related TEAEs and All STEAEs (Safety Population)

Adverse Event	*n* (%)
Any drug-related event by age cohort[a]	
Cohort 1: 6 mo–<1 y (*N* = 7)	0
Cohort 2: 1–<2 y (*N* = 11)	2 (18)
Cohort 3: 2–<6 y (*N* = 12)	0
Cohort 4: 6–<13 y (*N* = 27)	2 (7)
Cohort 5: 13–<18 y (*N* = 14)	1 (7)
Any drug-related event[a] (*N* = 71)	5 (7)
Neutropenia	2 (3)
Aspartate aminotransferase increased	1 (1)
Delirium	1 (1)
Eosinophilia	1 (1)
Insomnia	1 (1)
Left ventricular hypertrophy	1 (1)
Troponin I increased	1 (1)
Vomiting	1 (1)
Any STEAE by age cohort	
Cohort 1: 6 mo–<1 y (*N* = 7)	1 (14)
Cohort 2: 1–<2 y (*N* = 11)	2 (18)
Cohort 3: 2–<6 y (*N* = 12)	0
Cohort 4: 6–<13 y (*N* = 27)	8 (30)
Cohort 5: 13–<18 y (*N* = 14)	4 (29)
Any STEAE (*N* = 71)	15 (21)
Respiratory failure	2 (3)
Tachycardia	2 (3)
Bacteremia	1 (1)
Blood bilirubin increased	1 (1)
Brain herniation	1 (1)
Cellulitis	1 (1)
Cyclic vomiting syndrome	1 (1)
Encephalitis	1 (1)
Hypertension	1 (1)
Lactic acidosis	1 (1)
Multiorgan failure	1 (1)
Neutropenia	1 (1)
Pyrexia	1 (1)
Respiratory syncytial virus coinfection	1 (1)
Status epilepticus	1 (1)

[a] Drug-related events: study investigators assessed whether there was a reasonable possibility that the TEAE was caused by the study drug.

patients had viruses with amino-acid resistance substitutions at baseline (H3N2 V149A and H1N1pdm09 H275Y)[11,12]; these patients received 1 and 2 days of oseltamivir before the study, respectively. The V149A virus showed no phenotypic resistance relative to the reference strain. No resistance data were available for the H275Y virus because it could not be cultured.

DISCUSSION

In this study, we aimed to assess the safety and pediatric dosing of IV zanamivir in hospitalized pediatric patients with severe or progressive influenza. Overall, safety data were consistent with the profile expected in this population. Safety and efficacy results in children were similar to those previously described for adults. Relative to adults, fewer grade 3 or 4 TEAEs and STEAEs were reported (32% vs 44% and 21% vs 34%, respectively) in children; a lower incidence of mortality was also observed in children (7% vs 20%).[7] These findings are in line with previous observations that children hospitalized with influenza had better recovery than adults.[13]

No clinically significant trends were observed for ALT or total bilirubin levels in this pediatric patient population. This contrasts with results from the adult cohort study, in which protocol-defined liver events were reported in 13% of patients.[7] However, the adult patients were enrolled in the midst of the influenza pandemic, wereinfected primarily with H1N1pdm09, and were more severely ill than the pediatric patients.[7] No liver signal was seen in the controlled phase III trial of IV zanamivir conducted in adults and older adolescents (clinicaltrials.gov: NCT01231620).[8] The findings presented here support the hypothesis that the liver results in the adult cohort were related to the underlying disease or comorbidities.

Zanamivir exposure after pediatric dosing was generally within expectations on the basis of experience from phase I studies and results in hospitalized adults with influenza.[7] Mean serum zanamivir AUCs for pediatric patients with normal renal function were generally consistent with that seen in adults. The selected dosage adjustments (based on modeling) for age, weight, and renal function resulted in similar AUCs over a 12-hour dosing interval for twice-daily dosing. Exposure was similar for patients on ECMO, but the number of patients was small (n = 4).

Virologic findings in this study indicate that IV zanamivir treatment was likely associated with an antiviral effect, with a median reduction in viral load of 1.81 $\log_{10}$ copies per mL (from 6.66 $\log_{10}$ copies per mL at baseline) after 2 days of treatment, although the single-arm study design precludes comparing with antiviral kinetics from untreated patients. In the adult cohort, a reduction in viral load of 1.42 $\log_{10}$ copies per mL (from 5.34 $\log_{10}$ copies per mL at baseline) was observed.[7] These findings are also similar to those reported by researchers in previous studies of inhaled zanamivir.[5] Because this was not a placebo-controlled study, the impact of host immunity on the virologic

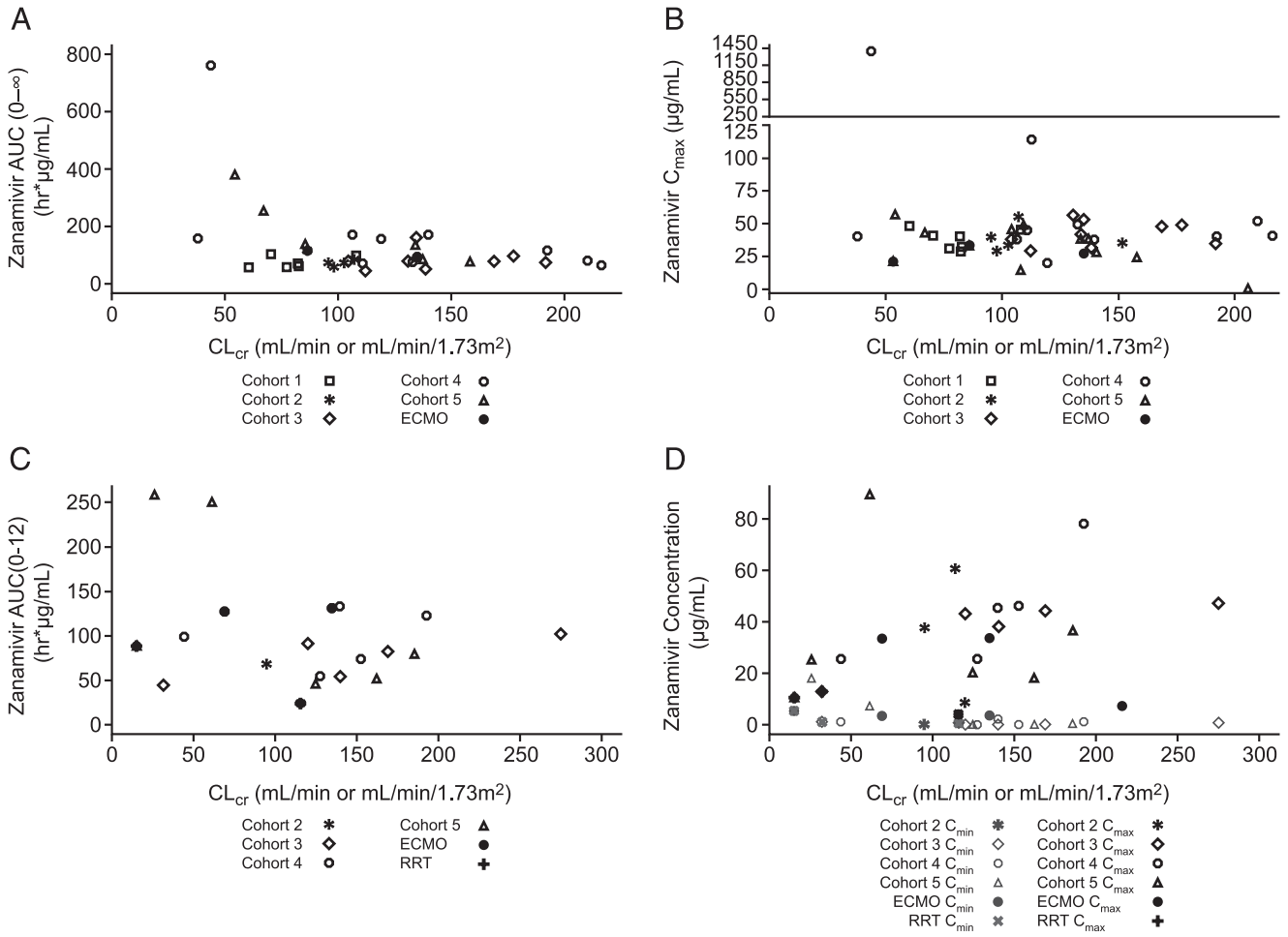

FIGURE 1

Zanamivir PK parameter estimates: A, Day 1 AUC ($_{0-\infty}$) versus CL_{cr}; B, Day 1 C_{max} versus CL_{cr}; C, Days 3 to 5 AUC ($_{0-12}$) versus CL_{cr}; D, Days 3 to 5 C_{max} and C_{min} versus CL_{cr}. The y-axis of panel B has been split to enable the visualization of an outlier data point. Cohort 1: 6 months to <1 year; Cohort 2: 1 to <2 years; Cohort 3: 2 to <6 years; Cohort 4: 6 to <13 years; Cohort 5: 13 to <18 years. Data from Fig 1 panels A and B are also presented in Supplemental Table 7, and data from Fig 1 panels C and D are also presented in Supplemental Table 8. AUC ($_{0-12}$), AUC over a dosing interval (τ) of 12 hour duration; AUC ($_{0-\infty}$), AUC from time 0 extrapolated to infinity; CL_{cr}, creatinine clearance; C_{max}, maximum serum concentration; C_{min}, trough serum concentration. CL_{cr} is reported in mL/min for patients ≥13 years as calculated by Cockcroft-Gault or in mL/min/1.73 m^2 for patients 6 months to <13 years as calculated by Schwartz equation.

response cannot be assessed. Furthermore, small sample sizes limit the ability to draw conclusions regarding the potential clinical relevance of previous oseltamivir use and treatment duration on viral load.

One specimen from an immunocompetent pediatric patient acquired an E119G mutation in the H1N1pdm09 NA gene at day 5. E119G is known to confer resistance to NA inhibitors.[10] The patient had been treated with oseltamivir for 3 days before the start of this study. No additional phenotypic data were available because the virus could not be cultured. This is possibly one of the first times that a resistance mutation has been identified from an immunocompetent patient treated with zanamivir.[5] The E119G substitution did not persist beyond day 5 and was therefore probably unfit and may have had minimal clinical impact. Treatment-emergent resistance substitutions occurred in 1.4% (1 out of 71) patients on the basis of the overall population, or 3.8% (1 out of 26) of patients with both baseline or day 1 and postbaseline or day 1 NA sequences. Similar levels of treatment-emergent NA resistance substitutions (E119D and E119E) occurred in the adult phase II study (1 out of 123 patients).[14] In the phase III study, 2 treatment-emergent resistance substitutions were detected in the 300 mg IV zanamivir arm (n = 163 influenza-positive patients), but none were detected in the 600 mg IV zanamivir arm (n = 162 influenza-positive patients).[8]

It is worth noting that 8 (11%) patients enrolled in this study were known to have received an influenza vaccine in the 9 months before the study. This is considerably lower than

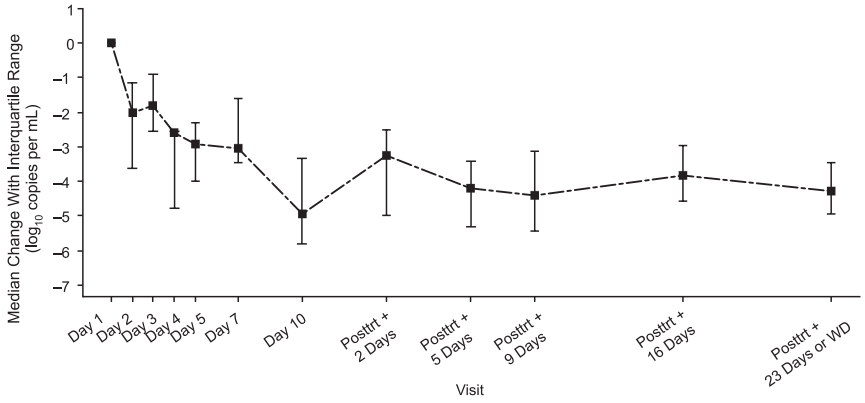

FIGURE 2

Median change from baseline in viral load (log_{10} copies per mL, NP samples) over time. One patient coinfected with A/H3N2 and B has viral loads for both viruses. One patient who received oseltamivir during the treatment period (2 days of IV zanamivir plus oseltamivir, 5 additional days of oseltamivir) was included in the viral load reduction analysis and this plot. The patient achieved undetectable viral load on day 2 of treatment. Posttrt, posttreatment; WD, withdrawal.

the mean US vaccination coverage seen for children in the 2013 and 2014 influenza season (58.9%).[15] In 2008, the Advisory Committee on Immunization Practices (United States) recommended that all children between the ages of 6 months and 18 years of age should be vaccinated against influenza.[16] This recommendation should have applied to most of the patients in this study because 93% were from the United States. Although the reasons for the lack of immunization in these patients is unclear and was not collected as part of this study, it underscores the possibility that vaccination could have prevented influenza infection or reduced the severity of symptoms.

One limitation of this study was that vital signs were recorded only once daily, which may have limited the reliability of the TTCR composite clinical endpoint. The single-arm, uncontrolled, open-label design of this study limited the ability to draw clear conclusions regarding efficacy above what may have been observed with no treatment. However, patients experienced generally favorable clinical outcomes given the degree of illness severity, with 42% on mechanical ventilation and 6% on ECMO at some point during the study. Similarly, viral load decreased during treatment despite high baseline viral loads and previous oseltamivir usage.

AEs, TEAEs, and STEAEs were assessed by the sponsor and the investigators. No patterns in the frequency and nature of the events were observed and no causal association with zanamivir was established. The results therefore support a favorable risk/benefit profile for IV zanamivir treatment of severe influenza in pediatric patients.

CONCLUSIONS

Overall, the safety profile of IV zanamivir was consistent with that expected in children with severe influenza, with no newly identified drug-related adverse safety findings. The majority of treated children experienced clinical improvement during the treatment course. Zanamivir exposure was similar to that measured in adults, supporting the pediatric dosing schedule that was adjusted for weight, age, and creatinine clearance.

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ABBREVIATIONS

ALT: alanine transaminase
AUC: area under the concentration-time curve
ECMO: extracorporeal membrane oxygenation
ET: endotracheal
ITT-E: intent-to-treat exposed
IV: intravenous
NA: neuraminidase
NP: nasopharyngeal
PCR: polymerase chain reaction
PK: pharmacokinetic
qRT-PCR: quantitative real-time polymerase chain reaction
STEAE: serious treatment-emergent adverse event
TEAE: treatment-emergent adverse event
TTCR: time to clinical response
ULN: upper limit of normal

interpretation and reviewed and revised the manuscript; Dr Adams was involved in reviewing and revising the manuscript, including the interpretation of statistical analyses; Ms Shortino conducted the analyses and was involved in reviewing and revising the manuscript, including the interpretation of statistical analyses; Drs Yates and Peppercorn contributed to the design of the study, analysis of the data, and interpretation of results and reviewed and revised the manuscript; Dr Munoz participated as one of the site's principal investigators, enrolled children into the trial, assisted in the review and analysis of data, and reviewed and revised the manuscript; Dr DeBiasi participated as one of the site's principal investigators, enrolled children into the trial, and reviewed and revised the manuscript; and all authors were involved in the analysis of study results, drafting of the initial manuscript, review and revision of the manuscript, and approved the final manuscript as submitted.

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