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Benefit of Early Oseltamivir Therapy for Adults Hospitalized With Influenza A: An Observational Study

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Background. Clinical guidelines recommend initiation of antiviral therapy as soon as possible for patients hospitalized with confirmed or suspected influenza.

Methods. A multicenter US observational sentinel surveillance network prospectively enrolled adults (aged ≥18 years) hospitalized with laboratory-confirmed influenza at 24 hospitals during 1 October 2022–21 July 2023. A multivariable proportional odds model was used to compare peak pulmonary disease severity (no oxygen support, standard supplemental oxygen, high-flow oxygen/non-invasive ventilation, invasive mechanical ventilation, or death) after the day of hospital admission among patients starting oseltamivir treatment on the day of admission (early) versus those who did not (late or not treated), adjusting for baseline (admission day) severity, age, sex, site, and vaccination status. Multivariable logistic regression models were used to evaluate the odds of intensive care unit (ICU) admission, acute kidney replacement therapy or vasopressor use, and in-hospital death.

Results. A total of 840 influenza-positive patients were analyzed, including 415 (49%) who started oseltamivir treatment on the day of admission, and 425 (51%) who did not. Compared with late or not treated patients, those treated early had lower peak pulmonary disease severity (proportional adjusted odds ratio [aOR]: 0.60, 95% confidence interval [CI]: .49–.72), and lower odds of intensive care unit admission (aOR: 0.24, 95% CI: .13–.47), acute kidney replacement therapy or vasopressor use (aOR: 0.40, 95% CI: .22–.67), and in-hospital death (aOR: 0.36, 95% CI: .18–.72).

Conclusions. Among adults hospitalized with influenza, treatment with oseltamivir on day of hospital admission was associated reduced risk of disease progression, including pulmonary and extrapulmonary organ failure and death.

Keywords. oseltamivir; antiviral therapy; influenza; severity; invasive mechanical ventilation; influenza-associated outcomes.

Since the influenza A(H1N1) pandemic in 2009, the use of influenza antiviral therapy, primarily the neuraminidase inhibitor oseltamivir, to treat hospitalized influenza patients has increased. Previous observational studies of this patient population found that receiving any antiviral treatment versus no treatment was associated with reduced risk of mortality [1–5] and shorter length of stay [5]. In addition, treatment initiated earlier in the course of illness, compared with later, may provide greater clinical benefit in terms of, reduced risk of

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mortality [6–13], shorter length of stay [12–14], reduced risk of 30-day hospital readmission [14], and reduced risk of complications such as hypoxia, pneumonia, and use of intensive forms of breathing support [11, 15, 16].

The 2018 Infectious Disease Society of America (IDSA) guidelines for patients hospitalized with suspected or laboratory-confirmed influenza recommend initiation of oseltamivir treatment as soon as possible, regardless of the time since symptom onset [17]. However, ongoing variability in the clinical use and timing of antiviral treatment [18], along with variation in the influenza virus strains circulating each year, could influence effectiveness. This study, conducted during the 2022–2023 influenza season in the United States, evaluated the clinical benefit of following clinical practice guidelines to treat adults hospitalized with acute influenza with oseltamivir as early as possible after hospital admission (on the day of hospital admission), compared with later or no treatment.

METHODS

Participants and Sites

Twenty-four hospitals from 19 US states within the Investigating Respiratory Viruses in the Acutely Ill (IVY) Network prospectively enrolled patients into an observational multi-pathogen acute respiratory illness (ARI) surveillance program from 1 October 2022 to 21 July 2023. The IVY Network is funded by the Centers for Disease Control and Prevention (CDC) and coordinated by the Vanderbilt University Medical Center. This program was determined to be a non-research public health surveillance activity by CDC and each participating site and was conducted in a manner consistent with applicable federal law and CDC policy (45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.).

Personnel at all sites followed a common protocol outlining eligibility criteria, data collection, and specimen collection procedures. Inclusion criteria were: (1) age ≥18 years; (2) hospital admission; (3) clinical presentation consistent with ARI, defined as having ≥1 of the following: fever, cough, shortness of breath, new hypoxemia, or new pulmonary findings on chest imaging consistent with pneumonia; and (4) a clinically obtained molecular or antigen test for influenza, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and/or respiratory syncytial virus (RSV) within 10 days of symptom onset (including an onsite clinical test before or while hospitalized, or an offsite "research" test on a specimen collected during hospitalization). For this analysis, patients testing positive for influenza were included. Exclusions were patients: (1) with a positive test for SARS-CoV-2 or RSV, including coinfections with influenza viruses; (2) receiving anti-influenza medications other than oseltamivir not indicated for hospitalized patients; and (3) who were discharged on the day of admission (ie, no follow-up for outcome assessment). In this analysis, no patients died on the day of admission.

Antiviral Treatment Exposure Groups

Enrolled patients hospitalized with influenza were classified into exposure groups based on the calendar day of treatment initiation. The decision to treat with oseltamivir was made by clinicians independent of the study protocol. Patients treated with oseltamivir on the day of admission were classified into an "early treatment" group. Patients not treated with oseltamivir on the day of hospital admission, including those who started oseltamivir later during hospitalization and those who never had oseltamivir started, were classified into a "late treatment/no treatment" group. The primary analysis compared patient outcomes in the early treatment group versus the late treatment/no treatment group. In a secondary analysis, patients never treated with oseltamivir were excluded, and patients with oseltamivir started on the day of hospital admission were compared to patients with oseltamivir started later in the hospital stay.

Outcomes

Pulmonary disease severity was classified using a 5-level ordinal scale: (1) no oxygen support, (2) standard supplemental oxygen therapy (flow rate <30 liters/minute), (3) high-flow nasal cannula or non-invasive ventilation, (4) invasive mechanical ventilation (IMV), and (5) all-cause in-hospital death. The scale was based on the World Health Organization (WHO) COVID-19 Clinical Progression Scale [19] and was previously used in this network to compare severity of vaccinated and unvaccinated cases of coronavirus disease 2019 (COVID-19) [20] and influenza [21]. Baseline severity was defined as the highest level the patient experienced on the day of hospital admission. Study outcomes were defined prospectively in the IVY case report form and statistical analysis plan, and based on events starting after the day of hospital admission (ie, after treatment group and baseline severity were established on the day of admission) and ending with hospital discharge. The primary outcome was peak pulmonary disease severity level the patient experienced during hospitalization. Secondary outcomes included: (1) hospital length of stay, (2) ICU admission, (3) initiation of extra-pulmonary organ support with vasopressors or new kidney replacement therapy, and (4) in-hospital death. Patients who already had the second or third outcomes on the day of admission were excluded from the respective analyses of those outcomes.

Statistical Analysis

Demographic and clinical characteristics of patients in the early treatment and late treatment/no treatment groups were compared using the Pearson χ^2 test for categorical variables or Wilcoxon rank-sum testing for continuous variables.

Additionally, we described changes in pulmonary disease severity level between baseline severity (highest level on the day of admission) and peak severity (highest level later during hospitalization) using counts and proportions of patients in 4 categories: peak lower than baseline (improvement), peak equal to baseline (no progression), peak 1 step higher than baseline (progression), and peak ≥2 steps higher than baseline (severe progression).

Analysis of the primary outcome, peak pulmonary disease severity, utilized a multivariable proportional odds model with peak pulmonary disease severity level as the dependent variable, treatment group (early treatment vs late/no treatment) as the primary independent variable, and the following covariables: baseline pulmonary disease severity level, age as a continuous variable, hospital site as a random effect, and sex and seasonal influenza vaccination status (vaccinated, unvaccinated, unknown) as additional categorical variables. After satisfying the proportional odds assumption from this model, an adjusted odds ratio (aOR) <1.0 indicated lower peak severity on the pulmonary disease severity ordinal scale in the early treatment group compared with the late/no treatment group. Secondary outcomes of ICU admission, vasopressor use or new kidney replacement therapy, and death were compared between the early treatment and late treatment/no treatment groups using multivariable logistic regression models, adjusted for the same covariables. Hospital length of stay was compared using a multivariable Cox proportional hazard regression model adjusted for the same covariables, in which an adjusted hazard ratio (aHR) >1.0 indicated higher likelihood of discharge (ie, shorter stay) in the early treatment group compared with the late/no treatment group. Sensitivity analyses were conducted for all outcomes by excluding patients never treated with oseltamivir in the hospital, thus comparing an early treatment group and a late treatment group. Analyses were conducted using SAS Version 9.4 (Cary, North Carolina, USA) [22].

RESULTS

Cohort

During the study period, 950 patients with influenza were enrolled; 110 patients were excluded from analysis, including 67 patients with coinfection with SARS-CoV-2 or RSV, 38 patients treated only with an anti-influenza agent other than oseltamivir, and 5 patients who were discharged on the day of admission (Supplementary Figure 1). No patients died on the day of admission. After exclusions, 840 patients were included in this analysis, including 415 (49%) who were in the early treatment group and 425 (51%) in the late treatment/no treatment group. The late treatment/no treatment group included 301 patients (36% of the overall population) with oseltamivir started after the day of admission (late treatment) and 124 patients (14% of the overall population) were not treated with oseltamivir (no treatment). Among late-treated patients, 234 (78%) had treatment initiated 1 day after admission, 32 (11%) 2 days after admission, and 35 (11%) ≥3 days after admission (Supplementary Figure 2).

Participant Characteristics

Age was distributed differently in the early treatment and late treatment/no treatment groups ($P = .016$), with a higher proportion of patients aged ≥75 years (27% vs 19%) and a lower proportion aged 65–74 years (20% vs 27%) in the early treatment group (Table 1). Patients in the early treatment group had higher baseline pulmonary disease severity ($P < .001$), including a lower proportion of patients not treated with any oxygen support on the day of admission (34% vs 56%). Oseltamivir was started sooner after symptom onset in the early treatment group (median 2 days; interquartile range [IQR]: 1–3 days) than those in the late treatment group (median 3 days; IQR 2–5 days) ($P < .001$). Although most patients tested positive for influenza on or before the day of admission, this was more frequent in the early treatment group (98%) than in the late/no treatment group (82%). A comparison of baseline characteristics of patients in the early treatment and late treatment groups (with the no treatment group excluded) is shown in Supplementary Table 1.

Primary Outcome

Patients in the early treatment group, compared with patients in the late treatment/no treatment group, were less likely to experience disease progression after the day of hospital admission, as measured by an escalation of disease severity on the pulmonary disease ordinal scale by 1 level (11% vs 21%, $P < .001$) or by ≥2 levels (3% vs 7%, $P = .027$) (Table 2). Time from admission to peak severity was distributed similarly among early treated and late treated/not treated patients (Supplementary Figure 2). In the proportional odds model of peak pulmonary disease severity after the day of hospital admission, patients in the early treatment group had lower severity compared with the patients in late treatment/no treatment group (proportional adjusted odds ratio [paOR]: 0.60, 95% confidence interval [CI]: .49–.72) (Figure 1).

Secondary Outcomes and Sensitivity Analyses

Patients in the early treatment group, compared with the late treatment/no treatment group, had a shorter hospital length of stay (median [IQR]: 4 days [2–7 days] vs 4 days [3–8 days], aHR for discharge: 1.19, 95% CI: 1.05–1.36), and lower odds of ICU admission (aOR: 0.25, 95% CI: .13–.49), acute vasopressor use or new kidney replacement therapy (aOR: 0.40, 95% CI: .22–.67), and in-hospital death (aOR: 0.36, 95% 0.19–0.69) (Table 3). Of the 14 in-hospital deaths recorded, 4 were in the early treatment group (1.0% of this group), 7 were in the late treatment group (2.3% of this group), and 3 were in the no treatment group (2.4% of this group). Although the timing of ICU

Table 1. Characteristics of Hospitalized Influenza Patients Receiving Oseltamivir on the Day of Admission (Early Treatment Group) Versus After the Day of Admission or Not at All (Late Treatment/No Treatment Group)—IVY Network, 1 October 2022–8 August 2023

Characteristic	Early Treatment (Oseltamivir on Day of Admission) (n = 415)		Late Treatment/No Treatment (Oseltamivir ≥1 d After Admission or Not Treated) (n = 425)		*P*-value (values <.05 in bold)
	n	%[a]	n	%[a]	
Days from illness onset to admission (median, IQR)	2 (1–3)		3 (2–5)[b]		**<.001**
Tested before or on the day of admission	408	98.31%	348	81.88%	**<.001**
Age category (years)					
18–49	100	24.10%	109	25.65%	**.0162**
50–64	124	29.88%	121	28.47%	
65–74	81	19.52%	114	26.82%	
75+	110	26.51%	81	19.06%	
Race and ethnicity					
White non-Hispanic	179	43.13%	212	49.88%	.154
Black non-Hispanic	131	31.57%	119	28.00%	
Hispanic	70	16.87%	55	12.94%	
Other	35	8.43%	39	9.18%	
Sex at birth					
Female	233	56.14	225	52.94	.351
Male	182	43.86	200	47.06	
Received current season influenza vaccination	121	44.32%	139	48.60%	.311
Influenza subtype					
Influenza A(H1N1)	81	37.67%	67	37.43%	.960
Influenza A(H3N2)	134	62.33%	112	62.57%	
Current smoker	91	24.86%	99	25.19%	.917
Immunocompromised[c]	60	14.46%	66	15.53%	.664
Chronic cardiovascular disease	269	64.82%	291	68.47%	.262
Chronic pulmonary disease	183	44.10%	182	42.82%	.710
Number of organ systems with a chronic medical condition[d]					
0	44	10.60%	37	8.71%	.563
1	92	22.17%	95	22.35%	
2	114	27.47%	116	27.29%	
3	90	21.69%	83	19.53%	
4+	75	18.07%	94	22.12%	
Highest pulmonary severity on the day of admission[e]					
No oxygen support	143	34.46%	237	55.76%	**<.001**
Standard (low-flow) oxygen therapy	208	50.12%	134	31.53%	
High-flow nasal cannula or non-invasive mechanical ventilation	45	10.84%	28	6.59%	
Invasive mechanical ventilation	19	4.58%	26	6.12%	
Other events on the day of admission					
Intensive care unit admission	45	10.84%	44	10.35%	.817
Initiation of vasopressor use or new kidney replacement therapy	18	4.34%	20	4.71%	.797

Abbreviation: IQR, interquartile range.

[a]Some percentages may reflect a different denominator due to missingness.

[b]Includes only those patients who received late treatment (n = 301).

[c]Any of: solid tumor or hematologic malignancy with immunosuppressive treatment in the previous 30 d, solid organ transplant with use of immunosuppressive medication in the previous 30 d, received bone marrow transplant/hematopoietic stem cell transplant within 2 y of transplantation or receipt of immunosuppressive therapy with the previous 30 d, not including CAR T-cell therapy, HIV infection with CD4 count <200 cells/mm^3 in the past 1 y or diagnosed with AIDS, congenital immunodeficiency syndrome, or current use of immunosuppressive therapy in the past 30 d for a condition other than malignancy, solid organ transplant, or bone marrow transplant/ hematopoietic stem cell transplant.

[d]Individual conditions were grouped into 7 categories: cardiovascular, neurologic, pulmonary, gastrointestinal, endocrine, renal, and hematologic. Participants were classified by the number of categories in which conditions were documented (0, 1, 2 or ≥3).

[e]Highest level of support received on the calendar day of admission.

admission was distributed similarly among early-treated and late-treated/not treated patients, acute kidney replacement or vasopressor use, and death all tended to occur earlier during hospitalization among the late-treated/not treated patients (Supplementary Figure 2). Sensitivity analyses of outcomes excluding patients who never received oseltamivir showed similar results to the primary analyses (Supplementary Table 2, Supplementary Table 3, Supplementary Figure 3).

Table 2. Change From Baseline to Peak Pulmonary Disease Severity Level Among Hospitalized Influenza Patients Treated With Oseltamivir on the Day of Admission (Early Treatment Group) Versus ≥1 Day After Admission or Not Treated (Late Treatment/No Treatment Group)—IVY Network, 1 October 2022 to 21 July 2023

	Early Treatment (Oseltamivir on Day of Admission) (n = 415)	%	Late Treatment/No Treatment (Oseltamivir ≥1 Day After Admission or Not Treated) (n = 425)	%	*P*-value (values <.05 in bold)
Progression on severity scale[a]					
Peak severity lower than baseline severity (Improvement after the day of admission without any progression)	35	8.4%	8	1.9%	**<.001**
Peak severity equal to baseline severity (no progression or improvement after the day of admission)	321	77.3%	300	70.5%	**.020**
Peak severity 1 level higher than baseline severity (progression)	45	10.8%	89	20.9%	**<.001**
Peak severity at least 2 levels higher baseline severity (severe progression)	14	3.4%	28	6.6%	**.027**

[a]The 5 levels on the ordinal pulmonary disease severity scale included: (1) no oxygen support, (2) standard supplemental oxygen therapy (flow rate <30 liters/minute), (3) high-flow nasal cannula or non-invasive ventilation, (4) invasive mechanical ventilation (IMV), and (5) in-hospital death. Baseline severity was defined as the highest severity level on the day of hospital admission. Peak severity level was defined as the highest severity level during the hospital course after the day of admission.

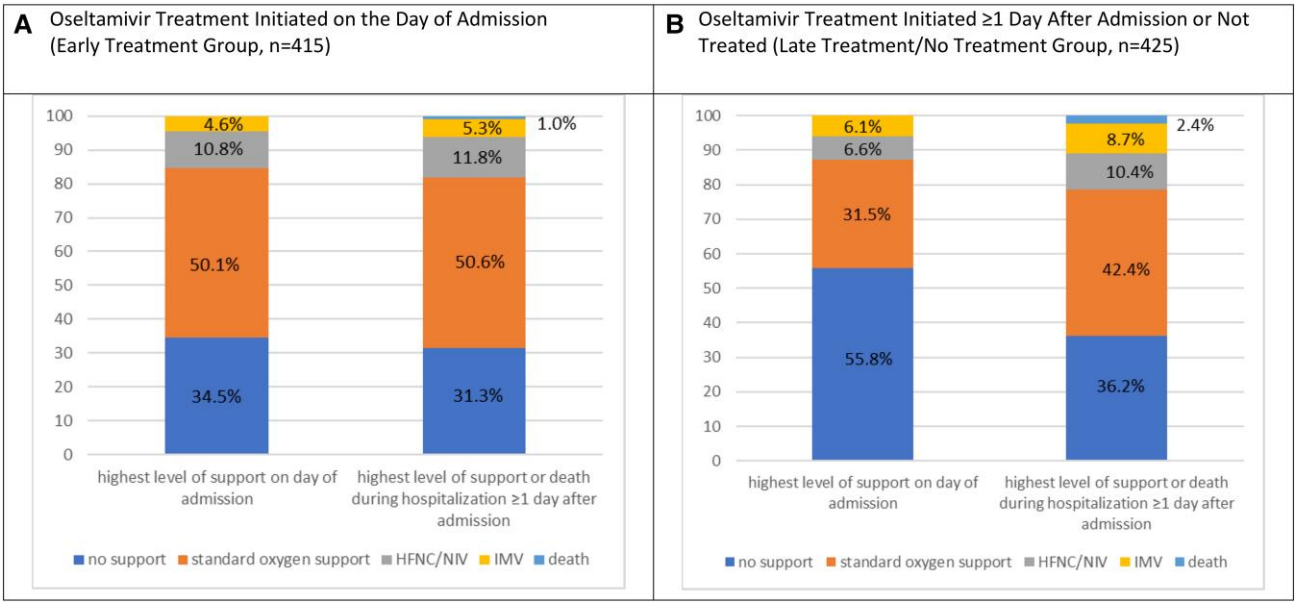

Figure 1. Pulmonary disease severity scale. Highest level of oxygen support or death on the day of admission (baseline) and during hospitalization ≥1 after admission among hospitalized influenza patients treated with oseltamivir on the day of admission (*A*) and treated ≥1 d after admission or not treated (*B*)—IVY Network, 1 October 2022 to 21 July 2023. While adjusting for baseline pulmonary disease severity, site, and age, patients initiating oseltamivir treatment on the day of admission had lower peak severity than those with oseltamivir initiated ≥1 d after admission or not treated (paOR: 0.60, 95% CI: .49–.72). Abbreviations: CI, confidence interval; HFNC, high flow nasal cannula; IMV, invasive mechanic ventilation; NIMV, noninvasive mechanic ventilation; paOR, propensity adjusted odds ratio.

DISCUSSION

Compared with patients who had oseltamivir started later during hospitalization or never initiated, those who had oseltamivir initiated on the day of hospital admission were less likely to experience a broad range of severe clinical outcomes during their hospital course, including progression of pulmonary disease severity, invasive mechanical ventilation, extrapulmonary organ failure, and in-hospital death. These results support the use of oseltamivir as soon as possible for adults hospitalized with influenza.

Although guidelines recommend treatment with an anti-influenza agent for adults hospitalized with influenza [15, 23], this study and other observational studies show that many hospitalized adults with influenza are not treated or have treatment initiated late. There are few randomized control trials (RCTs) of influenza antiviral medications due to the ethical problem of giving a placebo treatment to ill patients, and RCTs of hospitalized patients will likely remain rare despite some evidence of treatment benefit in previous

Table 3. Secondary Outcomes. Hospitalized Influenza Patients Treated With Oseltamivir on the Day of Admission (Early Treatment Group) Versus ≥1 Day After Admission or Not Treated (Late Treatment/No Treatment Group)—IVY Network, 1 October 2022–21 July 2023

	Early Treatment (Oseltamivir on Day of Admission) (n = 415)		Late Treatment/ No Treatment (Oseltamivir ≥1 Day After Admission or Not Treated) (n = 425)				
Event	n	%	n	%	Ratio	95% CI	*P*-value (values <.05 in bold)
Hospital length of stay, days (median, IQR])	4 (2–7)		4 (3–8)		1.19[a]	1.05–1.36	**.009**
Intensive care unit admission, n (%)[b]	18/370	4.9	50/381	13.1%	0.25[c]	.13–.49	**<.001**
Acute vasopressor use or kidney replacement therapy, n (%)[d]	28/397	7.1%	40/405	9.9%	0.40[c]	.22–.67	**.007**
In-hospital death, n (%)	4	1.0%	10	2.4%	0.36[c]	.19–.69	**.020**

Abbreviations: CI, confidence interval; IQR, interquartile range.

[a]Adjusted hazard ratio (aHR) is from a Cox proportional hazard regression for length of stay, adjusted for baseline pulmonary disease severity level on the day of admission, age, and site. An aHR >1.0 indicates faster hospital discharge (shorter length of stay) in the early treatment group compared with the late treatment/no treatment group.

[b]Patients admitted to ICU on the day of hospital admission were excluded from the analysis evaluating the ICU admission outcome (early treatment: n = 45; late treatment/no treatment: n = 44).

[c]Adjusted odds ratio (aOR) is from logistic regression, adjusted for baseline pulmonary disease severity level on the day of admission, age, and site. An aOR <1.0 indicates the outcome was less common in the early treatment group compared with the late treatment/no treatment group.

[d]Patients with acute vasopressor use or kidney replacement therapy initiated on the day of hospital admission were excluded from the analysis evaluating the acute vasopressor use or kidney replacement therapy outcome (early treatment: n = 18; late treatment: n = 20).

trials [24, 25]. Although platform trials initiated during the COVID-19 pandemic to evaluate antiviral and other treatments of COVID-19, such as REMAP-CAP [26] and RECOVERY [27], have now added influenza antiviral treatment arms and offer large sample sizes, they also lack placebo groups, may comprise substantial variations in care between sites, and may not assess clinical outcomes in detail [28]. Observational studies such as the current study, despite potential residual confounding, offer an important opportunity for triangulation by leveraging granular clinical data to show that early oseltamivir treatment may lessen disease progression and severe influenza–associated outcomes.

The reasons why many patients hospitalized with influenza have delayed antiviral treatment or no treatment are not fully understood, but clinicians could be less likely to prescribe antiviral treatment when more than 48 hours have elapsed since a patient's illness onset [29]. A 48-hour window is often used to identify ambulatory outpatients who may have a beneficial response to antiviral treatment in terms of symptom duration. However, this 48-hour treatment window does not generalize well to in-hospital settings where some reduction in viral replication—even if not optimal—may be of particular benefit to hospitalized patients who may have prolonged viral replication and higher risk of organ failure and death [30]. In this analysis and another recent study [18], median time from influenza illness onset to hospital admission was 3 days, suggesting that many hospitalized patients are unlikely to meet the 48-hour outpatient treatment window. This study and prior studies [4, 6, 7] suggest that there is some treatment benefit for oseltamivir among adults hospitalized with influenza even when initiated >48 hours after symptom onset and that initiation of treatment as early as possible likely maximizes that benefit.

Our findings are consistent with and build upon previous studies. The observed modest reduction in hospital length of stay in early treated patients was similar to that observed other studies [5, 12–14]. In addition, our findings of lower likelihood of ICU admission and acute kidney replacement therapy or acute vasopressor use among early treated patients were similar to a previous study that found protection against a composite of influenza complications that included these outcomes in early-treated patients (compared with late-treated) patients [15]. Finally, our finding of reduced likelihood of in-hospital death associated with early oseltamivir treatment was similar to the substantial reduction in mortality associated with early treatment during earlier influenza seasons [5, 6, 9, 10, 13].

This study had several strengths. First, the study design included prospective patient enrollment, 24 geographically dispersed US sites, and influenza testing of all participants at the same central laboratory. Second, our results captured elements of severity reduction (eg, non-progression among hospitalized patients with relatively mild illness) not previously observed in studies focused on single severe outcomes, such as mortality. Third, as the current study was conducted during a single, influenza A(H3N2) virus-predominant influenza season (2022–2023), it provides data on the effectiveness of oseltamivir against a recent influenza A(H3N2) virus strain.

Finally, although all observational studies evaluating effectiveness of therapeutics have potential biases, including indication bias and immortal time bias, our design took steps to mitigate these potential biases. All results were adjusted for disease severity on the day of hospital admission, age, sex, site, and influenza vaccination status, to mitigate potential indication bias. Immortal time bias, in which patients who receive a

treatment are also less likely to have poor outcomes because they survived long enough to receive treatment, is present in some observational studies [31]. Similar to how a clinical trial would be designed, we defined the window for initiation of oseltamivir treatment as beginning on the calendar day of hospital admission and the window for outcome ascertainment starting with the day after hospital admission and ending with hospital discharge, thus standardizing the windows for treatment initiation and outcome ascertainment. Although the study question of whether early initiation of oseltamivir therapy after hospital admission benefits adults hospitalized with influenza is only relevant for patients who survive to hospital admission, no patients in the study died on the day of hospital admission. In analyses for other secondary outcomes (ie, ICU admission and kidney replacement therapy/vasopressor use), the exclusion of patients who had already the outcome on the day of admission increases the likelihood of the outcome occurring ≥1 day after admission; however, this bias is present in both the early treatment and late treatment/no treatment comparator groups.

Our results should be interpreted with consideration of several limitations. First, influenza severity and antiviral effectiveness may differ by influenza type or subtype [32, 33], and the results observed here may not be generalizable to seasons during which influenza A(H1N1)pdm09 or B viruses are predominant. Second, our study was not sufficiently powered to examine a variety of oseltamivir treatment initiation timepoints at which to assess clinical effectiveness or identify a potential maximum time-to-treatment threshold for effectiveness against illness progression or severe outcomes. In addition, the size of the untreated patient group was insufficient to conduct separate sensitivity analyses comparing no treatment to early or late treatment. Third, there were some potentially relevant variables that were not collected, including outpatient antiviral treatment prior to hospital admission, or other treatments (ie, with macrolides, statins, corticosteroids, or immunomodulators) before or during hospitalization. In addition, other clinical metrics that were unavailable due to study design (eg, virologic replication measures, antiviral resistance emergence, side effects) or influenza season dynamics (eg, lack of influenza B cases) could potentially enhance understanding and interpretation of the findings and should be considered in future research. Fourth, time points for symptom onset, hospital admission, and treatment initiation were based on 1-day intervals without more specific timing, such as to the hour. Classifying early oseltamivir treatment as initiation on the day of admission was designed to identify if oseltamivir was included in the initial hospital-based treatment plan for the patient, including treatments initiated in the emergency department and those in initial admission orders. Finally, despite our statistical approach including adjustment for baseline disease severity, age, site, sex, and influenza vaccination status, residual confounding in the relationship between early initiation of oseltamivir and clinical outcomes is possible.

CONCLUSION

In a 24-hospital network in the United States during the 2022–2023 influenza season, among adult patients hospitalized with influenza, early treatment with oseltamivir started on the same day as hospital admission was associated reduced risk of disease progression, including pulmonary and extrapulmonary organ failure and death. These findings support current recommendations, such as the IDSA Influenza Clinical Practice Guidelines and CDC guidance, to initiate oseltamivir treatment as soon as possible for adult patients hospitalized with influenza.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

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