Clinical Infectious Diseases

EDITORIAL COMMENTARY

Oseltamivir Treatment of Influenza in Children

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(See the Major Article by Malosh et al on pages 1492–500.)

Annual seasonal influenza epidemics cause substantial disease burden among children worldwide [1–4]. In the United States, influenza disease burden among children is highest in those aged < 5 years, with the highest hospitalization rates typically in young infants [5–8]. Children with chronic medical conditions are at increased risk for complications, although hospitalizations and influenza-associated deaths also occur in previously healthy children, highlighting a need for improved prevention and control efforts [9, 10].

In late 2000, the neuraminidase inhibitor (NAI) oseltamivir was approved by the Food and Drug Administration (FDA) for antiviral treatment of uncomplicated influenza within 2 days of illness onset in children aged ≥1 year in the United States. In late 2012, the FDA approved oseltamivir for treatment of influenza within 2 days of illness onset in children aged ≥14 days. Oseltamivir is available as the prodrug oseltamivir phosphate and converted by the liver to the active metabolite oseltamivir carboxylate. The mechanism of action of oseltamivir carboxylate and other NAIs is to interfere with the release of influenza viral particles from infected host cells by binding to influenza viral neuraminidase, resulting in reduced spread of influenza viruses in the respiratory tract [11]. There has been ongoing debate about interpretation of the evidence base for oseltamivir as reported in randomized placebo-controlled trials and observational studies [12–16].

In this issue, Malosh et al. report the findings of a meta-analysis of 5 randomized placebo-controlled trials (RCTs) of early oseltamivir treatment (initiated within 2 days of illness onset) of influenza-like-illness (ILI) and uncomplicated influenza in pediatric outpatients [17]. Three included RCTs enrolled otherwise healthy children and those with chronic conditions, and 2 RCTs were conducted among children with asthma. The primary endpoint assessed was illness duration. In 3 RCTs, illness resolution was defined as time from starting treatment to the following for at least 24 hours: returning to normal activities without fever, cough, or rhinitis or only with mild symptoms; and in 2 RCTs, illness duration was defined as time from starting treatment to resolution of symptoms or of major signs and symptoms. In children with laboratory-confirmed influenza (intention-to-treat-infected [ITTi]), early oseltamivir treatment significantly reduced illness duration by 17.6 hours versus placebo. In a stratified analysis of the ITTi population comprised of asthmatic children in 2 studies, there was no benefit of oseltamivir treatment. For the 3 RCTs not restricted to asthmatic children, oseltamivir treatment significantly reduced illness duration by 29.9 hours. In a pooled analysis of the ITTi population without asthma, oseltamivir treatment reduced illness duration by 34.9 hours. In another pooled analysis, oseltamivir treatment started within 24 hours of onset reduced illness duration significantly more than when started 24–48 hours after onset (22.8 vs. 4.4 hours).

Among the ITTi population, there was a 34% reduction in risk of otitis media with oseltamivir treatment versus placebo. Although there were fewer cases of lower respiratory tract complications >48 hours after starting oseltamivir treatment versus placebo in the ITTi population, this difference was not significant. The frequency of hospitalization was too low to draw inferences. There was a significantly higher relative risk (RR) of vomiting with oseltamivir treatment (RR: 1.63, 95% confidence interval [CI]: 1.30, 2.04), but no increased risk of nausea, diarrhea, or severe adverse events, or withdrawal from treatment.

Disagreement exists about the relevant study population of interest in the oseltamivir treatment RCTs. Some studies have focused upon all participants with a nonspecific influenza-like illness syndrome (ITT population), whereas most studies have considered the findings for the ITTi population. Oseltamivir is not known to have any antiviral effects against noninfluenza respiratory viruses that can cause influenza-like illness. The oseltamivir (TAMIFLU) package insert approved by the FDA states that "There is no evidence for efficacy of TAMIFLU in any illness caused by pathogens other than influenza viruses [18]." Therefore, reporting of ITT results is biased against finding clinical benefit because any treatment effect for influenza virus infection is attenuated by including participants who tested negative for influenza. This

Received 13 December 2017; editorial decision 20 December 2017; accepted 3 January 2018; published online January 5, 2018.

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Clinical Infectious Diseases® 2018;66(10):1501–3

DOI: 10.1093/cid/cix1150

is illustrated by the meta-analysis findings of a greater reduction in illness for the ITTi population (point estimate 17.6 hours) versus only 8.4 hours for the ITT population. Furthermore, in the pooled analysis, no effect of oseltamivir treatment was found for participants who tested negative for influenza.

The meta-analysis found that the clinical benefit was greatest (except for children with asthma) when oseltamivir treatment was started within 24 hours after illness onset, highlighting the importance of starting treatment soon after illness onset. There are huge challenges to implementing such timely administration of oseltamivir treatment to children with influenza. Recent studies in the United States reported that persons who experience acute respiratory illness and are at high risk for influenza complications, including young children, often do not present to medical care within 2 days of illness onset [19–21]. A recent global meta-analysis of observational data for 1747 pediatric outpatients aged <16 years with comorbidities considered to be at high risk for influenza complications and who had laboratory-confirmed influenza A(H1N1)pdm09 virus infection reported that NAI treatment (mostly oseltamivir) was associated with reduced odds of hospital admission versus no treatment (adjusted odds ratio [OR] 0.25, 95% CI, 0.18–0.34, $P < .001$) [22]. However, in a US study over a 5-year period, only about one-quarter of high-risk children who presented within 2 days of illness onset with reverse transcription polymerase chain reaction (RT-PCR)-confirmed influenza received a prescription for NAI treatment [22]. This indicates a major need for educating parents and clinicians about the importance of early diagnosis and initiation of oseltamivir treatment of influenza in children, but other strategies are needed to facilitate early oseltamivir treatment of children with influenza.

The Malosh et al. meta-analysis did not address oseltamivir treatment of children with influenza who present >48 hours after illness onset. In a post hoc analysis of participants that were enrolled 3 days after illness onset in an RCT conducted among participants (median age 5 years) in urban Bangladesh, the duration of major signs or symptoms in those treated with oseltamivir was significantly shorter by 1 day compared with placebo [23]. Additionally, for participants enrolled 3 days after illness onset, the proportion of patients with influenza virus isolated on days 2 and 4 after illness onset was significantly lower in those treated with oseltamivir compared with placebo. This suggests that there is still benefit of initiating oseltamivir treatment for influenza patients 3 days after illness onset.

It is puzzling why early oseltamivir treatment of influenza would provide benefit to children without asthma but not to those with asthma. The authors suggest that the clinical endpoints used to assess efficacy in children with underlying respiratory conditions might not be sufficient to distinguish the clinical benefit of oseltamivir, and that other objective endpoints such as improvement in pulmonary function and virological benefit might be more appropriate. In the only published RCT of early oseltamivir treatment in asthmatic children aged 6–12 years with laboratory-confirmed influenza, oseltamivir treatment significantly improved forced expiratory volume at 1 second versus placebo (10.8% vs. 4.7%, $P = .0148$) and significantly reduced asthma exacerbations up to day 7 (51% vs. 68%, $P = .031$), indicating that oseltamivir treatment provided some clinical benefit [24]. At a minimum, more extensive studies with measurable endpoints are needed to assess the impact of oseltamivir treatment of influenza in children with asthma.

The biggest gap not addressed by the meta-analysis remains the evidence base for oseltamivir treatment of influenza in hospitalized patients. The only published randomized placebo-controlled trial of oseltamivir treatment in hospitalized children with influenza was terminated early with only 21% of the targeted population enrolled and concern that length of hospitalization may have been due at times to nonclinical factors [25]. Some observational studies in children and adults hospitalized with influenza have reported clinical benefit of early (within 48 hours of illness onset) versus later initiation or treatment versus no treatment, but have been criticized for inherent biases [16]. One large pooled meta-analysis reported survival benefit of NAI treatment compared with no treatment in hospitalized adults with influenza but not in children [26]. However, most influenza-related hospitalizations in children are of short duration, and in-hospital mortality is uncommon compared with adults. Although oseltamivir is FDA-approved for early treatment of uncomplicated influenza in outpatients, the American Academy of Pediatrics and the Centers for Disease Control and Prevention also recommend it for treatment of hospitalized children of all ages with influenza [27, 28]. Despite these recommendations, antiviral treatment of hospitalized children with influenza varies widely. One study reported that during 2007–2015, 69% of children hospitalized with influenza at 46 children's hospitals received antiviral treatment (99% oseltamivir), with a range of 38%–83% per hospital [29]. Another study reported that antiviral treatment of hospitalized patients with laboratory-confirmed influenza increased during 2010–2015, and overall 72% of pediatric patients received antiviral treatment, with the largest increase over time in young children aged <1 year [30].

Perhaps the only way to settle the debate about oseltamivir treatment benefit in hospitalized influenza patients is to conduct a large placebo-controlled RCT. Because the duration of hospitalization is shorter and in-hospital mortality is low among most children with influenza in comparison with adults, different endpoints, outcomes, and numbers of estimated participants are needed for studies in children than in adults. However, identifying the best endpoints for studies in hospitalized influenza patients remains very challenging [31]. Furthermore, such RCTs would likely need to be conducted outside the

United States because use of placebo could be construed as unethical since oseltamivir treatment is recommended for all hospitalized influenza patients in the United States. These studies would require collaboration across many clinical sites worldwide for several years to achieve the high enrollment needed, would be very costly, and it is unclear who would fund such studies. It is doubtful that any placebo-controlled RCTs of oseltamivir treatment in hospitalized influenza patients will be implemented because other influenza therapeutics with different mechanisms of action than NAIs are in development [32].

Until there are other approved drugs with mechanisms of action different than that of NAIs for treatment of influenza, oral oseltamivir will continue to be the most widely available and recommended antiviral for early treatment of influenza in outpatients and hospitalized pediatric patients. Taken together, the clinical benefits of early oseltamivir treatment of influenza reported by Malosh et al., and in observational studies of patients with laboratory-confirmed influenza, outweigh the risk of vomiting, including in young infants.

Notes

Disclaimer. The views expressed are those of the author and do not necessarily represent the official policy of the Centers for Disease Control and Prevention.

Potential conflicts of interests. The author reports no potential conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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