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Short Article

Safety and tolerability of a 6-week course of oseltamivir prophylaxis for seasonal influenza in children

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In an open-label study, 49 children aged 1–12 years received oseltamivir (30–75 mg once daily depending on bodyweight) for 6 weeks for influenza prophylaxis. Seventeen participants reported 22 adverse events (AEs); in three participants, AEs were considered probably drug related (nausea or vomiting). No serious AEs were reported. The tolerability profile was similar to pooled safety data from treatment studies (duration of 5 days) in children.

Keywords Children, influenza, oseltamivir, prevention, prophylaxis.

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Influenza is common and often serious in children. During annual epidemics, infection rates may exceed 30% in preschool and school-age children[1] and can reach 50% in day care settings.[2] A quarter of those infected will develop acute otitis media,[3,4] while upper or lower respiratory tract infections such as sinusitis and pneumonia[3–6] and central nervous system complications[7] can also occur. Despite this, vaccination coverage remains suboptimal,[8] which places a considerable burden on healthcare services, particularly at the outpatient level.[9] Children were also disproportionately affected in the recent H1N1 influenza pandemic, with children aged <4 years suffering a high rate of hospitalization.[10,11]

Oseltamivir (Tamiflu®; Roche, Basel, Switzerland) is an antiviral for the treatment and post-exposure prophylaxis (PEP) of seasonal and pandemic influenza in children aged ≥1 year and infants <1 year infected with pandemic influenza. The standard courses of treatment (twice-daily dosing) and PEP (once-daily dosing) last for 5 and 10 days, respectively. Longer durations of oseltamivir prophylaxis may be useful in high-risk individuals who have not received or cannot receive influenza immunization during periods of increased influenza activity and when vaccine strains are poorly matched to circulating viruses. Whereas prophylaxis for 6 weeks is efficacious and well tolerated in adults,[12,13] it has yet to be evaluated in children in a community setting. The current study investigated the safety and tolerability of a 6-week course of oseltamivir prophylaxis against seasonal influenza in children aged 1–12 years.

This open-label multicenter trial (ClinicalTrials.gov identifier: NCT00412555) was undertaken at centers in the USA and Canada at the request of the US Food and Drug Administration (FDA) and complied with the principles of the Declaration of Helsinki, local regulations and Good Clinical Practice Guidelines. The trial protocol was approved by independent ethics committees prior to study commencement. Written, informed consent was provided by every child or their parent/guardian. Boys and pre-menarcheal girls aged 1–12 years were enrolled when surveillance data from the US Centers for Disease Control and Prevention or Public Health Agency of Canada indicated that influenza was circulating locally. Children with influenza-like illness (ILI) or confirmed influenza (by rapid diagnostic test) at baseline were excluded, as were those with creatinine clearance <30 ml/min per 1·73 m^2, those with uncontrolled renal, vascular, neurologic, metabolic, or pulmonary disease, or those with known chronic renal failure, hepatitis, or cirrhosis. Children who had received either live influenza vaccination or antiviral treatment in the 2 weeks before enrollment were excluded. All participants received oseltamivir once daily for 6 weeks as a suspension or (for some children weighing >40 kg) as capsules. Dose was calculated according to body weight: ≤15 kg, 30 mg; >15–23 kg, 45 mg; >23–40 kg, 60 mg;

>40 kg, 75 mg. After baseline screening and assessment, participants were assessed on day 21, at treatment end (day 42), and at follow-up on day 70. Unscheduled clinic visits were allowed if participants felt unwell. Safety endpoints were as follows: incidence of adverse events (AEs) on treatment (up to 2 days after stopping treatment), vital signs, physical examination results, and serum chemistry and hematology results. Reverse transcriptase polymerase chain reaction (RT-PCR) and viral culture were used to test for influenza virus in nasal and throat swabs taken at baseline and at any illness visits, and serum antibody titer (hemagglutination inhibition assay) was measured at baseline and on days 42 and 70.

Fifty-two subjects (26 boys and 26 girls) were enrolled between December 18, 2006, and May 23, 2007. Three children did not return for the post-baseline safety assessment and were therefore excluded from the safety population (n = 49), whose baseline demographics are summarized in Table 1. Seventeen (35%) participants reported a total of 22 AEs, most commonly gastrointestinal disorders (six events in six participants) or infections and infestations (seven events in six participants); these are listed in Table 2. Twelve events were mild, eight were moderate, and two (otitis media and toothache) were severe. No serious AEs were recorded. Three participants (6%) had at least one AE (nausea or vomiting) considered probably related to treatment by the investigator. Eight participants in the safety population discontinued treatment, two because of AEs, that is, nausea (considered probably treatment related) and oral mucosal blistering (not treatment related), and six for a non-safety reason (refused treatment/withdrew consent). Compliance was good: 39/49 (80%) received ≥80% of the expected cumulative dose and completed ≥5 weeks of treatment. Physical examinations were normal throughout the study, and no clinically relevant changes in vital signs or laboratory results were recorded. Influenza infection was not detected by RT-PCR in any subject. Elevated antibody titers (≥fourfold higher than baseline) were detected in six participants (12%), of whom four were asymptomatic and two had limited symptoms (cough and coryza) that did not meet the criteria for clinical illness (defined as fever and cough and/or coryza). Six participants had ILI not caused by influenza virus.

Table 1. Baseline characteristics of all children in the safety population (n = 49)

Characteristic	Value
Sex, *n* (male/female)	23/26
Age at enrollment, years, mean (range)	7·8 (1–12)
Aged <5 years, *n*	9
Aged ≥5 years, *n*	40
Weight kg, mean (range)	32·48 (9·1–67·5)
Height cm, mean (range)	128·3 (76·0–152·0)
Received inactivated influenza vaccination, *n* (yes/no)	3/46

Table 2. Number and proportion of participants reporting on-treatment adverse events in the safety population (n = 49)

	Participants, *n* (%)
Total with at least one adverse event	17 (35)
Gastrointestinal disorders	
Total with at least one event	6 (12)
Nausea	2 (4)
Vomiting	2 (4)
Dental caries	1 (2)
Oral mucosa blistering	1 (2)
Infections and infestations	
Total with at least one event	6 (12)
Tonsillitis	2 (4)
Nasopharyngitis	1 (2)
Otitis media	1 (2)
Otitis media acute	1 (2)
Sinusitis	1 (2)
URTI	1 (2)
Respiratory, thoracic and mediastinal disorders	
Total with at least one event	3 (6)
Asthma	1 (2)
Tonsillar hypertrophy	1 (2)
Wheezing	1 (2)
Eye disorders	
Total with at least one event	2 (4)
Eye swelling	1 (2)
Eyelid irritation	1 (2)
Injury, poisoning and procedural complications	
Total with at least one event	2 (4)
Contusion	1 (2)
Joint sprain	1 (2)
Ear and labyrinth disorders	
Ear pain	1 (2)
Musculoskeletal disorders	
Tendonitis	1 (2)

To our knowledge, this is the first report of extended (6-week) oseltamivir prophylaxis in children aged 1–12 years in a community setting. Although our study was small in scale and lacked a control group, the prophylactic regimen was well tolerated and no serious AEs were reported. AEs were considered to be probably related to treatment for three participants, one of whom discontinued because of the event (nausea). This safety and tolerability profile is consistent with pooled safety data in >1000 children who received oseltamivir 2 mg/kg twice daily for 5 days, in which the AE profile was similar to placebo,[14] and that in 32 immunocompromised children, adolescents, and adults who received oseltamivir prophylaxis for

8 weeks.[15] A higher incidence of AEs was reported in a retrospective survey of 247 children aged 11–12 years who received oseltamivir for 10 days for PEP during the H1N1 2009 influenza pandemic.[16] Possible reasons for the difference in reporting rate include the population studied, the retrospective nature of the study, and the non-clinical setting. Although elevated antibody titers were found in six participants, laboratory-confirmed clinical influenza was not detected in any subject. In this small study in children aged 1–12 years, oseltamivir prophylaxis for 6 weeks was well tolerated.

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Conflict of Interest

Lisa Cupelli and Regina Dutkowski are employees of, and hold stocks in, Hoffmann-La Roche, Inc.

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