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Oseltamivir in seasonal influenza: cumulative experience in low- and high-risk patients

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Seasonal influenza viruses cause annual disease epidemics that affect individuals at low and high risk for secondary illnesses. Influenza vaccines are widely used in high-risk patients to prevent infection, but the protection afforded varies by population; uptake is also limited in some groups. Antiviral drugs for influenza are now readily available. Oseltamivir is the most widely used antiviral for the treatment and prophylaxis of seasonal influenza, and its efficacy and safety are now well established in a variety of populations. In addition to decreasing the severity and duration of the symptoms of influenza, clinical and epidemiological studies demonstrate that oseltamivir significantly reduces the frequency of secondary illnesses and exacerbation of underlying conditions; survival is also significantly improved in seriously ill patients who are hospitalized with severe influenza. Resistant viruses are isolated with a low frequency during oseltamivir treatment (0.33% in adults and 4.0% in children among almost 2000 oseltamivir-treated patients enrolled onto Roche-sponsored clinical trials of oseltamivir treatment during the oseltamivir development programme). However, an oseltamivir-resistant influenza A (H1N1) virus emerged in Europe during the 2007–08 season and circulated in the southern and northern hemispheres in 2008–09. No link with oseltamivir usage could be detected, and the clinical impact of these viruses was limited. Oseltamivir-susceptible pandemic (H1N1) 2009 viruses now predominate in many countries. Oseltamivir is generally well tolerated, with a similar adverse event profile to placebo.

Keywords: treatment, prophylaxis, efficacy, safety

Introduction

Seasonal influenza viruses continue to impose a substantial disease burden on individuals at low and high risk for secondary illnesses. In the USA, the CDC estimates that between 5% and 20% of the population may become infected during each influenza season,[1] and similar rates have been reported in Europe and Asia.[2,3] As a result of seasonal influenza, ~36000 deaths and 226000 hospitalizations are estimated to occur in the USA each year, the majority of which involve the very young (<2 years), the elderly (≥65 years) and those with co-morbid conditions, such as chronic pulmonary, cardiovascular and metabolic disorders.[4,5] These patients are considered at high risk for influenza-associated complications, which may include sinusitis, pharyngitis, bronchitis, pneumonia, croup and otitis media.[5] Lower risk populations are also susceptible to influenza and its complications, and these patients may be responsible for a sizeable proportion of the societal and healthcare costs associated with the disease.[6–8]

It is widely accepted that vaccination is the most effective way of minimizing the disease burden of influenza.[4] When well matched to circulating strains, inactivated and live attenuated influenza vaccines provide between 80% and 100% protection against infection.[9] However, the protection afforded is known to be influenced by patient characteristics, with the very young, the frail elderly and those with co-morbid conditions often deriving only limited benefit.[9] Efficacy is also compromised when the circulating viruses are a poor match for those included in the vaccine.[4] Vaccination programmes may also be poorly established or of limited scope in some countries,[10] while in those with more comprehensive policies uptake can be suboptimal in defined patient groups.[11,12] For these reasons, large numbers of patients who are at risk for the potentially serious complications of influenza continue to be susceptible to infection. As such, there is a pressing need for effective treatment options.

In the USA, the CDC recommends the antiviral neuraminidase inhibitors oseltamivir and zanamivir (rather than amantadine or rimantadine from the older adamantane class) for the treatment of seasonal influenza in individuals presenting to medical care with symptoms of <48 h duration (Table 1).[4] Although not considered a substitute for vaccination, antiviral prophylaxis is also recommended for high-risk individuals and other patient groups when the risk of infection is high (Table 1). These

Table 1. CDC recommendations for the use of neuraminidase inhibitors in seasonal influenza[4]

Treatment of laboratory-confirmed influenza (commencing within 48 h of symptom onset)	Prophylaxis during periods of increased influenza activity
• hospitalized patients (even if started after 48 h) • individuals with confirmed influenza pneumonia • persons with bacterial co-infection • individuals at high risk of influenza-related complications • low-risk individuals who want to decrease the duration and severity of their symptoms and limit their chances of transmitting influenza to others at high risk of complications	• persons at high risk during the 2 weeks after influenza vaccination • individuals for whom influenza vaccination is contraindicated • family members or healthcare providers who are likely to be exposed to people at high risk, unvaccinated individuals or infants aged <6 months • high-risk individuals, their close contacts and healthcare workers when vaccines are poorly matched to circulating strains • healthcare providers involved in a response to an institutional influenza outbreak involving residents at high risk (e.g. nursing home)

recommendations are generally reflected in the most recent advice on antiviral use from the Infectious Diseases Society of America (IDSA)[13] and in European national guidelines, although no pan-European recommendations currently exist.[14] Of the two neuraminidase inhibitors, oseltamivir has been most widely used in clinical practice, with >65 million treatment courses prescribed worldwide (Roche, data on file).

Oseltamivir treatment in seasonal influenza

Clinical trials in low- and high-risk groups

The efficacy of oseltamivir in the treatment of influenza has been widely evaluated in randomized, controlled studies involving children ≥1 year and adults of all ages. In the pivotal trials of oseltamivir in low-risk adolescents and adults aged ≥13 years, patients with influenza-like illness were randomized to twice-daily treatment with 75 or 150 mg of oseltamivir or placebo.[15,16] Compared with placebo, oseltamivir significantly reduced the duration of illness by 25%–32% ($P \leq 0.05$) and the severity of symptoms by 18%–38% ($P < 0.02$) in patients with laboratory-confirmed influenza ($n = 374$ and 475, respectively).[15,16] A subsequent investigation demonstrated a significant correlation ($P < 0.0001$) between the duration of illness and the time of oseltamivir initiation, such that commencement within 12 h of symptom onset reduced illness duration by 3.1 days more than initiation at 48 h (illness duration: 108 h versus 182.6 h).[17] In the study described by Treanor et al.,[16] the incidence of physician-diagnosed secondary complications was significantly reduced in the active treatment group ($P = 0.03$ versus placebo), as was the frequency of antibiotic usage. In a pooled analysis of 10 clinical trials involving 2413 patients (13–97 years) with influenza-like illness who received 75 mg of oseltamivir or placebo twice daily, active treatment significantly reduced the incidence of influenza-related lower respiratory tract complications requiring antibiotics by 55% ($P < 0.001$ versus placebo). The incidence of such complications in high-risk patients was also significantly reduced ($P = 0.02$, Table 2).[18]

A number of clinical studies have explored the use of oseltamivir treatment in children. In one trial, children aged 1–12 years with influenza-like illness of <48 h received twice-daily oseltamivir (2 mg/kg) or placebo for 5 days.[19] Compared with placebo, oseltamivir significantly reduced symptom duration in those with laboratory-confirmed influenza ($n = 452$) by 36 h ($P < 0.0001$), and the extent and severity of illness by 29% ($P = 0.002$). Reductions were also seen in the incidence of complications, especially otitis media (44% reduction versus placebo), and antibiotic prescriptions were significantly less frequent (31% versus 41% on placebo; $P = 0.03$).[19] Using the same treatment regimen, Johnston et al.[20] randomized asthmatic children aged 6–12 years with influenza-like illness to oseltamivir or placebo. Oseltamivir treatment led to a reduction in illness duration for those with laboratory-confirmed influenza ($n = 179$) of 10.4 h (8%), although this was not significant ($P = 0.5420$ versus placebo). However, significant benefits were observed in terms of pulmonary function (improvement in forced expiratory volume at 1 s of 10.8% versus 4.7% with placebo; $P < 0.02$) and asthma exacerbations up to day 7 (68% versus 51% of patients remained within 20% of the highest peak flow rate; $P = 0.03$; Table 2).[20] Off-label use of oseltamivir in infants <1 year has also been evaluated. Tamura et al.[21] compared outcomes in infants <1 year ($n = 47$) with those in older children (1–15 years) with influenza, who either received 5 days of oseltamivir treatment started within 48 h of symptom onset ($n = 486$) or did not ($n = 95$). The duration of fever in the oseltamivir-treated infant group (2.7 ± 1.7 days) was similar to that in the older group who received oseltamivir (2.5 ± 2.1 days), and significantly shorter than that in the untreated group (4.2 ± 3.8 days; $P < 0.0001$). Further data in German infants also indicate that oseltamivir treatment may be efficacious in this population.[22]

Several clinical investigations have examined the benefit of oseltamivir treatment in high-risk patient groups. A pooled analysis of data from the oseltamivir clinical trial programme revealed that oseltamivir treatment significantly reduced the duration of illness among patients with chronic cardiac diseases by 32% versus placebo ($P < 0.05$) and by 30% in those with respiratory disease ($P < 0.01$ versus placebo).[23] Data from individual studies are presented in Table 2. Lin et al.[24] explored the efficacy of oseltamivir in Chinese patients with chronic respiratory or cardiac diseases. Patients with influenza-like illness received 75 mg of oseltamivir twice daily for 5 days or symptomatic therapy. In patients with laboratory-confirmed influenza ($n = 56$), oseltamivir significantly reduced illness duration (by 36.8%) and severity (by 43.1%) versus symptomatic therapy ($P = 0.0479$ and $P = 0.0002$, respectively). The incidence of complications and antibiotic use was also significantly reduced ($P = 0.0053$ and $P = 0.0167$ versus symptomatic therapy, respectively).

In a prospective cohort study, McGeer et al.[25] assessed the impact of antiviral therapy on the outcomes of patients hospitalized with severe influenza in southern Ontario, Canada. In their

Table 2. Effect of treatment with oseltamivir on complications of influenza in high-risk patients

Study	Treatment regimen	Population (number of patients analysed)	Outcome in patients with laboratory-confirmed influenza		
			outcome	incidence	P value
Kaiser et al.[18] 2003	75 mg of oseltamivir twice daily versus placebo	high-risk adolescents and adults (n=769)	lower respiratory tract complications	12.2% with oseltamivir versus 18.5% with placebo	0.02
Johnston et al.[20] 2005	2 mg/kg oseltamivir twice daily versus placebo	children aged 6–12 years with asthma (n=179)	improvement in pulmonary function	10.8% with oseltamivir versus 4.7% with placebo	0.0148
			asthma exacerbations	68% of oseltamivir recipients within 20% of peak flow versus 51% with placebo	0.031
Lin et al.[24] 2006	75 mg of oseltamivir twice daily versus symptomatic therapy	adolescents and adults with cardiac or respiratory diseases (n=56)	complications antibiotics	11% with oseltamivir versus 45% with control 37% with oseltamivir versus 69% with control	0.0053 0.0167
Lee et al.[27] 2009	75 mg of oseltamivir twice daily versus no antiviral	hospitalized adults aged >16 years with influenza (n=147)	viral shedding	10.2% culture positive at ≥4 days post-symptoms with oseltamivir versus 38.5% with no antiviral; culture positive at ≥5 days: 4.2% versus 21.2%	0.002 (≥4 days); 0.006 (≥5 days)
McGeer et al.[25] 2007	75 mg of oseltamivir twice daily versus no antiviral	hospitalized adults with influenza (n=327)	mortality	odds ratio with oseltamivir versus no antiviral: 0.21 (95% CI 0.06–0.80)	0.02
		hospitalized adults aged ≥65 years with influenza (n=227)	mortality	odds ratio with oseltamivir versus no antiviral: 0.24 (95% CI 0.06–0.92)	not reported
Chemaly et al.[29] 2006	75 mg of oseltamivir twice daily versus no antiviral	immunocompromised stem cell transplant recipients aged ≥1 year with influenza A (n=72)	pneumonia mortality	12% with oseltamivir versus 48% with no antiviral 0% with oseltamivir versus 38% with no antiviral	<0.05 0.001

CI, confidence interval.

JAC

study, 327 adults admitted to Toronto Invasive Bacterial Diseases Network (TIBDN) hospitals with laboratory-confirmed influenza were enrolled between 1 January 2005 and 31 May 2006. Of these, 103 patients received oseltamivir. Compared with those who did not receive antivirals, oseltamivir treatment was associated with a significant reduction in 15 day mortality in all patients {odds ratio (OR) 0.21 [95% confidence interval (CI) 0.06–0.80]; $P = 0.02$} and in those aged ≥ 65 years [OR 0.24 (95% CI 0.06–0.92)].[25] In a second surveillance study by the same group, oseltamivir treatment was shown to be a significant predictor of survival in patients with laboratory-confirmed influenza who were admitted to intensive care units within the TIBDN [OR 3.2 (95% CI 1.5–7.0)].[26] In a 1 year, prospective, observational study, Lee et al.[27] evaluated viral loads and factors affecting viral clearance in 147 persons hospitalized with severe influenza A (H3N2). Oseltamivir treatment started on or before symptom day 4 was independently associated with an accelerated decrease in viral RNA concentration and viral RNA clearance at 1 week. The same group also conducted a prospective, observational study in two general hospitals in Hong Kong during 2007 and 2008.[28] All participants were inpatients aged ≥ 18 years and had laboratory-confirmed influenza. In total, 760 patients were studied, and most were of older age (mean 70 years), had underlying medical conditions (60%) and were hospitalized with complications (78%). Of these, 395 (52%) were treated with oseltamivir (77.7% within 2 days of symptom onset). Antiviral use was associated with reduced in-hospital mortality (3.8% versus 6.0% for patients on no antiviral), when adjusted for time to presentation and complications.[28]

A number of uncontrolled studies have also investigated the use of oseltamivir in immunocompromised patients. In a retrospective study in adults with haematological malignancies who had undergone haematopoietic stem cell transplantation (HSCT), the incidence of pneumonia was significantly lower in 72 patients infected with influenza A treated with oseltamivir (12% versus 48%; $P < 0.05$ versus no antiviral).[29] A similar finding was observed in patients infected with influenza B, and no patient who received neuraminidase inhibitor therapy died from influenza, compared with three of eight (38%) patients who did not ($P = 0.001$). Further studies in HSCT patients have confirmed the efficacy of oseltamivir in preventing illness progression and death,[30,31] and positive outcomes have also been noted in leukaemia[32] and bone marrow transplant patients.[33]

Epidemiological studies in low- and high-risk groups

The efficacy of oseltamivir in treating influenza and preventing its complications has been analysed using epidemiological data collected through various US health insurance databases (Table 3). One such investigation used the MarketScan Health Insurance Claims Database to evaluate the incidence of influenza-associated complications in children, adolescents and adults during the 2000–05 influenza seasons.[34] Claims outcomes were collected for influenza patients who received oseltamivir and compared with a matched control group who did not receive antivirals ($n = 31674$ per group). Compared with the no-antiviral group, significant reductions were detected with oseltamivir for the risk of developing secondary pneumonia (15%), respiratory illnesses (20%) and otitis media and its complications (31%). Oseltamivir was also associated with significant

Table 3. Epidemiological studies of the effect of oseltamivir treatment on complications of influenza

Study	Database	Population (number of patients who received oseltamivir; no antiviral)	Outcome	Adjusted RR, HR or OR[a]	Reduction in risk versus no antiviral cohort
Barr et al.[36] 2007	MarketScan, 2000–04 seasons	children aged 1–12 years ($n = 4447$; 20407)	pneumonia antibiotic use	RR 0.483 (0.326–0.717) RR 0.741 (0.691–0.795)	51.7% not presented
Nordstrom et al.[37] 2005	Ingenix, 1999–2002 seasons	children aged ≥ 1 year, adolescents and adults ($n = 11632$; 60427)	pneumonia antibiotic use hospitalization	HR 0.72 (0.60–0.86) HR 0.89 (0.86–0.93) HR 0.74 (0.61–0.90)	28% 11% 26%
Gums et al.[38] 2008	PharMetrics Patient-Centric Database, 2001–06 seasons	children, adolescents and adults ≤ 65 years ($n = 45751$; 45751)	pneumonia otitis media hospitalization	RR 0.89 (0.80–1.00) RR 0.84 (0.77–0.91) RR 0.71 (0.62–0.83)	11% 16% 29%
		children aged 0–5 years ($n = 3804$; 3849)	otitis media	not presented	21%
		children aged 6–12 years ($n = 6560$; 6601)	pneumonia otitis media	not presented not presented	36% 30%

Peters et al.[34] 2008	MarketScan, 2000–05 seasons	children, adolescents and adults (n=31674; 31674)	pneumonia	RR 0.85 (0.73–0.98)	15%
			respiratory illnesses	RR 0.80 (0.76–0.83)	20%
			otitis media	RR 0.69 (0.61–0.79)	31%
			hospitalization	RR 0.62 (0.52–0.74)	38%
			hospitalization due to respiratory illness	RR 0.43 (0.27–0.69)	57%
		children aged ≤12 years (n=7772; 7389)	pneumonia	RR 0.47 (0.33–0.66)	53%
			respiratory illnesses	RR 0.72 (0.65–0.80)	28%
			otitis media	RR 0.61 (0.54–0.71)	39%
			hospitalization	RR 0.50 (0.31–0.81)	50%
			hospitalization due to respiratory illness	RR 0.09 (0.01–0.70)	91%
		children aged 1–2 years (n=1303; 1379)	pneumonia	RR 0.48 (0.24–0.99)	52%
			respiratory illnesses	RR 0.69 (0.54–0.87)	31%
			otitis media	RR 0.68 (0.52–0.88)	32%
		children aged 3–5 years (n=1820; 1961)	respiratory illnesses	RR 0.74 (0.59–0.92)	26%
			otitis media	RR 0.71 (0.53–0.95)	29%
		children aged 6–12 years (n=4649; 4049)	pneumonia	RR 0.43 (0.26–0.71)	57%
			respiratory illnesses	RR 0.80 (0.75–0.85)	20%
			otitis media	RR 0.71 (0.54–0.95)	29%
Blumentals and Schulman[35] 2007	MarketScan, 2000–06 seasons	adolescents aged ≥13 years and adults (n=36751; 36751)	respiratory diseases	HR 0.82 (0.79–0.86)	18%
			otitis media	HR 0.77 (0.65–0.93)	23%
			hospitalization	HR 0.78 (0.67–0.91)	22%
Orzeck et al.[42] 2007	MarketScan, 2000–06 seasons	high-risk adults aged ≥18 years with diabetes (n=2919; 6171)	respiratory illnesses	RR 0.83 (0.73–0.93)	17%
			hospitalization	RR 0.70 (0.52–0.94)	30%
Piedra et al.[39] 2009	MarketScan, 2000–06 seasons	high-risk children with underlying medical conditions (n=1634; 3721)	respiratory illnesses other than pneumonia	14 day HR 0.74 (0.63–0.8) 30 day HR 0.87 (0.77–0.97)	26% 13%
			otitis media and its complications	14 day HR 0.69 (0.48–0.99) 30 day HR 0.70 (0.53–0.92)	31% 30%
			all-cause hospitalization	14 day HR 0.33 (0.13–0.83) 30 day HR 0.49 (0.27–0.89)	67% 51%
Majid et al.[40] 2009	Insurance database, May 2000–September 2006	adults aged ≥18 years (n=49238; 102692)	stroke or transient ischaemic heart attack	HR 0.72 (0.62–0.82)	28%
Casscells et al.[41] 2009	TRICARE military patient database, October 2003–September 2007	high-risk adults aged ≥18 years with a history of cardiovascular disease (n=6784; 30698)	recurrent cardiovascular events	OR 0.417 (0.349–0.498)	60%

RR, relative risk; HR, hazard ratio; OR, odds ratio.

[a]Differences between the oseltamivir and control groups were considered statistically significant if the 95% confidence interval did not include 1.

decreases in the risk of hospitalization for any reason (38%) and, in particular, due to respiratory illnesses (57%). Parallel outcomes were noted using the same database in analyses of adults and adolescents aged $\geq$13 years,[35] and children aged 1–12 years; a significant reduction in antibiotic usage was also noted.[36] Data from other health claims sources also indicate that oseltamivir treatment is associated with significantly reduced incidences of pneumonia, hospitalization and other complications, and antibiotic use (Table 3).[37,38] In children with underlying medical conditions registered on the MarketScan database, oseltamivir was associated with significant reductions in the risks of respiratory illnesses other than pneumonia, otitis media and its complications, and all-cause hospitalization in the 14 and 30 day periods after influenza diagnosis.[39]

Medical and pharmaceutical claims data recorded between May 2000 and September 2006 have also been used to compare the incidence of stroke or transient ischaemic attack (TIA) in the 6 months after influenza diagnosis in patients $\geq$18 years prescribed either oseltamivir (n=49238) or no antiviral treatment (n=102692).[40] Oseltamivir treatment was associated with a 28% reduction in risk of stroke or TIA [hazard ratio 0.72 (95% CI 0.62–0.82)]. Significant reductions in risk were also detected within 1 and 3 months of the diagnosis and in patients aged <65 years (34% reduction within 6 months) and $\geq$65 years (51% reduction within 1 month). A more recent database study examined 37482 military health system beneficiaries aged $\geq$18 years with a history of cardiovascular (CV) disease and a subsequent diagnosis of influenza from 1 October 2003 to 30 September 2007.[41] Subjects were grouped according to whether or not they had received oseltamivir within 2 days of their influenza diagnosis. The incidence of recurrent CV events within 30 days of influenza diagnosis was significantly lower among oseltamivir-treated subjects than those who did not receive oseltamivir (8.5% versus 21.2%; P<0.005). Using a propensity-scored logistic regression model, a statistically significant reduction in CV events with oseltamivir treatment was found [OR 0.417 (95% CI 0.349–0.498)]. In a study of the MarketScan database, claims data from the 2000–06 influenza seasons were screened to assess the influence of oseltamivir on the risk of complications in adults $\geq$18 years with diabetes.[42] Compared with no antiviral therapy (n=6171), patients on oseltamivir (n=2919) had a significantly reduced risk of respiratory illnesses (17% reduction) or hospitalization for any illness (30% reduction) (Table 3).

Prophylaxis with oseltamivir in seasonal influenza

Oseltamivir post-exposure prophylaxis (PEP) in households

The efficacy of oseltamivir as PEP in households has been examined in two randomized controlled trials involving both low- and high-risk subjects. Following a successful randomized trial involving individuals aged $\geq$12 years within households in North America and Europe,[43] a second household study including children $\geq$1 year as well as adults and elderly subjects was undertaken.[44] Index cases (n=298) started oseltamivir treatment following the onset of influenza-like illness, and household contacts were randomized by household to once-daily oseltamivir PEP for 10 days (n=410) or twice-daily oseltamivir treatment

for 5 days on the emergence of influenza-like illness in the individual (n=402, of whom 52 received treatment) at recommended doses. Excluding participants with laboratory-confirmed influenza at study start, 228 contacts in the PEP group and 248 contacts in the treatment group were exposed to 184 index cases with laboratory-confirmed influenza. Compared with the treatment-only arm, the protective efficacy of oseltamivir PEP against laboratory-confirmed influenza was 84.5% for individual contacts (P=0.002; Figure 1) and 78.8% for households (P=0.0008).[44] The incidence of laboratory-confirmed influenza in paediatric contacts aged 1–12 years (n=117) was analysed separately and was reduced by 80.1% in the PEP group compared with the treatment-only group (4% versus 21%, respectively; P=0.0206; Figure 1).

Oseltamivir seasonal prophylaxis

In two studies of identical design, the efficacy of influenza prophylaxis with oseltamivir in low-risk adults (aged 18–65 years) in the USA during the 1997–98 influenza season was explored.[45] Subjects were randomly assigned to 75 mg of oseltamivir (taken once or twice daily; n=520 for both groups) or placebo (n=519) for 42 days (6 weeks). Due to a low incidence of laboratory-confirmed influenza in both studies, the studies were pooled to provide sufficient power to evaluate efficacy. The proportion of subjects with laboratory-confirmed influenza was significantly lower in each of the oseltamivir groups than in the placebo group (1.2% and 1.3% versus 4.8%; P<0.001 and P=0.001, respectively). Protective efficacy with oseltamivir was 76% in the once-daily arm and 72% in the twice-daily arm. In another study, the protective efficacy of oseltamivir prophylaxis among frail elderly individuals (aged $\geq$65 years) in nursing homes during the 1998–99 northern hemisphere season was considered.[46] Participants received 75 mg of oseltamivir or placebo once daily for 6 weeks, and were vaccinated against influenza in accordance with care home policy. In total, 548 residents were enrolled, of whom 80% were vaccinated. The incidence of laboratory-confirmed clinical influenza was significantly lower in those randomly assigned to oseltamivir (n=276) than the
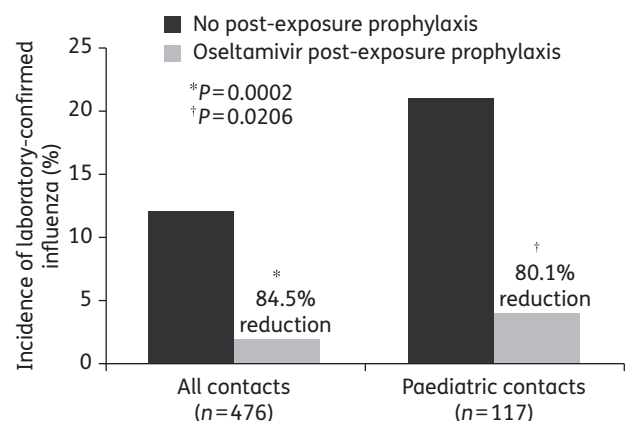

Figure 1. Incidence of laboratory-confirmed influenza infection in household contacts without influenza at baseline who did or did not receive oseltamivir post-exposure prophylaxis (commenced within 48 h of symptom onset). Figure derived from data in Hayden et al.[44]
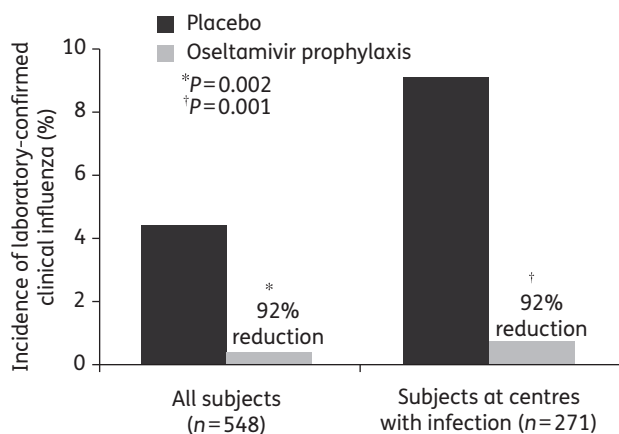
Figure 2. Incidence of laboratory-confirmed clinical influenza in elderly nursing home residents who received 6 weeks of seasonal prophylaxis with oseltamivir or placebo. Figure derived from data in Peters et al.[46]

272 subjects on placebo (0.4% versus 4.4%, respectively; P=0.002), a reduction of 92% (Figure 2).[46] Oseltamivir prophylaxis provided a similar protective efficacy whether subjects had been vaccinated or not. The protective efficacy of oseltamivir prophylaxis was a secondary endpoint in an open-label study involving children 1−12 years.[47] Weight-based unit doses (30−75 mg) of oseltamivir were taken once daily for 42 consecutive days (6 weeks). Although not powered to determine efficacy, no cases of laboratory-confirmed influenza were recorded in the 49 children who received oseltamivir.

A randomized, double-blind, placebo-controlled study of oseltamivir prophylaxis has recently been conducted in immunocompromised patients. In this trial, adults and children receiving solid organ (liver and/or kidney) or allogeneic HSCTs (n=470) received 12 weeks of oseltamivir or placebo.[48] The primary endpoint was the proportion of subjects with clinical influenza and positive viral culture and/or a ≥4-fold rise in antibody titre from baseline. Safety and tolerability and the incidence of resistant virus were also assessed. Data presented from this trial suggest that although the primary study endpoint was not met, active treatment was associated with a significant reduction in the incidence of laboratory-confirmed influenza by RT−PCR or viral culture. Oseltamivir was well tolerated and no resistant virus was detected.

Resistance to oseltamivir among seasonal influenza viruses

Resistance in the clinical trial programme

In the 3 years prior to the introduction of oseltamivir (1996−99), no influenza viruses with reduced susceptibility to oseltamivir were detected in global surveillance by the Neuraminidase Inhibitor Susceptibility Network (NISN).[49] Pooled data from almost 2000 oseltamivir-treated patients during the oseltamivir clinical treatment programme showed that drug-induced resistance occurred with a low incidence (0.33% in adults and 4.0% in children) (Table 4).[50] The higher level of resistance among children was linked to the 2 mg/kg flat dose employed in the paediatric studies, which led to the formulation of a weight-based unit

dosing schedule for children. No resistance was detected in any of the prophylaxis studies in adults and children. Resistance mutations were found in influenza A viruses only and were specific to virus subtypes; the most frequent mutations in N2 viruses were R292K and E119V, whereas the most frequent in N1 viruses was H275Y (often referred to as H274Y, which accords to N2 numbering).[50]

In clinical trials, oseltamivir-resistant virus occurred only transiently in viral samples shed by patients,[51,52] emerging on study days 4 or 6 and clearing by day 8 in adults and day 10 in children.[50] In one study,[53] resistant viruses were detected in 2 of 54 oseltamivir-treated adults inoculated with H1N1. In both patients, the onset of resistance was associated with a transient spike in viral shedding that subsided by day 7. No differences were seen between the clinical signs and disease course of patients carrying resistant viruses and of those carrying wild-type virus.[19,54] Animal models used to characterize some of the resistant virus strains isolated during the clinical trial programme found that all of these isolates were less fit than wild-type strains in some way.[55−60] In particular, the H275Y mutant not only showed poorer transmission but also had to be given at a dose 100 times greater than that of the wild-type virus to produce an infection in donor animals.[58]

Resistance before 2007: surveillance

Consistent with pre-treatment samples taken before the start of clinical trials,[50] surveillance during 1996−99, before oseltamivir and zanamivir were introduced, showed no evidence of naturally occurring resistance.[49] Resistance remained at a low level after the introduction of the neuraminidase inhibitors. Between 1999 and 2002, only 8 of 2287 (0.35%) influenza A and B viral isolates showed reduced susceptibility (>10 times lower than the mean for the virus subtype for the year in question), and none of these was from patients known to have received a neuraminidase inhibitor.[61] Only one of the eight isolates carried a known resistance mutation (H275Y)—the others carried different variations in the neuraminidase. Similarly, analysis of 1050 influenza virus isolates from the 2000−01 and 2001−02 seasons did not identify any isolate with any of the four 'signature' amino acid mutations in neuraminidase known to confer resistance to oseltamivir or zanamivir [at positions 119, 152, 274 or 292 (N2 numbering)].[62]

More recently, the NISN reported an analysis of influenza virus isolates from 74 public health laboratories in Japan during the four seasons from 2003−04 to 2006−07.[63] Although oseltamivir use in Japan is substantially higher than in any other country (5−9 million prescriptions per season, with 5%−10% of the population treated annually), resistance was found in no more than one of the viral subtypes tested (A/H1N1, A/H3N2 and B) in any single season, and its incidence was low (0.3%−2.2%). Moreover, there was no apparent increase in the incidence of resistance in Japan, and no evidence of progressive accumulation of any resistant subtype. Surveillance of seasonal influenza in 22 European countries over the same period by the European Surveillance Network for Vigilance against Viral Resistance (VIRGIL) also found that <1% of strains in each season had reduced susceptibility to oseltamivir.[64] The incidence of viruses with reduced susceptibility in global surveillance of resistance mutations between 2004 and 2007 was also very low (12/3261, 0.4%),[65] although these included a new mutation (R371K) with high levels of resistance to both oseltamivir and zanamivir.

Table 4. Incidence of resistant virus and associated mutations in Roche-sponsored clinical studies of oseltamivir in naturally acquired influenza infection[50]

Roche clinical trial number (published reference if applicable)	Population	Oseltamivir dose (twice daily)	Incidence of resistant virus/total number of isolates analysed
Adolescents and adults			
WV15670/WV15671 (Nicholson et al.[15], Treanor et al.[16])	healthy adults 18–<65 years	75 mg; 150 mg	2/211 (75 mg); 2/207 (150 mg)
M76001	healthy adolescents and adults ≥13 years	75 mg	0/496
WV15812	at-risk adolescents and adults ≥13 years	75 mg	0/61
WV15819	at-risk elderly patients ≥65 years	75 mg	0/34
WV15730	healthy adults 18–<65 years	75 mg	0/7
WV15707	at-risk elderly nursing home residents	75 mg	0/3
JV15823 (Kashiwagi et al.[95])	healthy Japanese adults ≥16 years	75 mg	0/88
Children and adolescents			
WV15731	healthy children 1–12 years	3 mg/kg	0/5
WV15758 (Whitley et al.[19])	healthy children 1–12 years	2 mg/kg	10/183
WV15759/WV15871	at-risk asthmatic children 6–12 years	2 mg/kg	0/60
NV16871 (Johnston et al.[20])	at-risk asthmatic children 6–12 years	30, 45 or 60 mg depending on body weight and age	2/26
NV16871 (unpublished)	at-risk asthmatic adolescents 13–17 years	30, 45 or 60 mg depending on body weight and age	0/17
JV16284 (unpublished)	healthy Japanese children 1–12 years	2 mg/kg	7/43
Households			
WV16193 (Hayden et al.[44])	healthy adults and children ≥1 year	75 mg (adults); 30, 45 or 60 mg depending on body weight (children)	0/121 (adults); 0/147 (children)
Totals			adults: 4/1228 (0.33%) children: 19/481 (4.0%)

Stephenson et al.[66] evaluated the emergence of resistant virus during treatment with the recommended oseltamivir dosages in 64 children aged 1–12 years with influenza. In this study, oseltamivir-resistant viruses were recovered from 3 of 11 children infected with influenza A (H1N1), 1 of 34 children with A (H3N2) and 0 of 19 children with influenza B. No evidence of prolonged illness was detected in children infected with drug-resistant virus.

Resistance after 2007: surveillance

Preliminary results from analysis of 2007–08 isolates showed a rise in the incidence of A/H1N1-H275Y viruses compared with previous seasons (57/896 isolates, 6.4%), mostly in the USA.[65] Confirming this unexpected trend, the European Influenza Surveillance Scheme reported that the overall prevalence of H1N1 viruses resistant to oseltamivir was 23% (586/2533 isolates tested),[67] while the VIRGIL network put the incidence over the entire season at 20%, but with large differences between countries, e.g. 68% in Norway, 10% in the UK and 1% in Italy.[68] Importantly, the majority of circulating H1N1 viruses in Europe remained susceptible to oseltamivir (Figure 3),[69] as was the case in the USA. In the subsequent southern hemisphere winter in 2008, high levels of resistant H1N1 virus were seen in South Africa (100% of 225 isolates tested) and Australia (93% of 76 isolates tested), although rates were lower in South
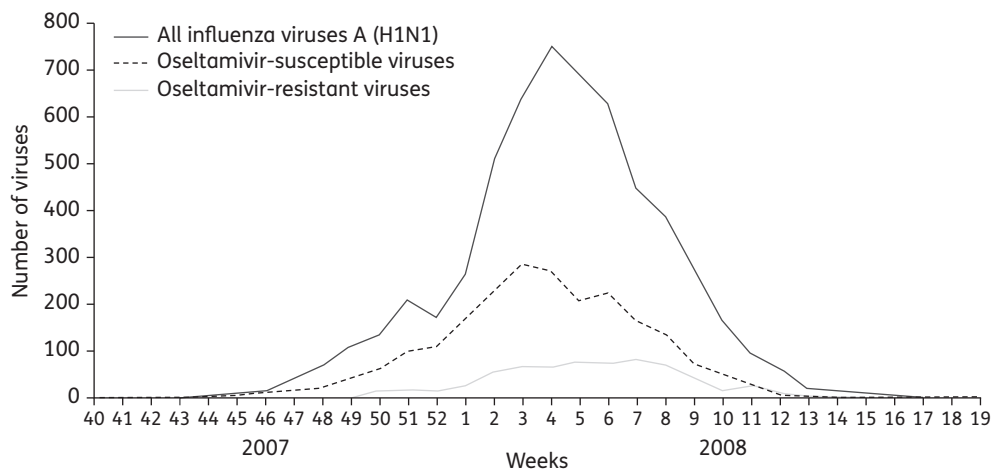
Figure 3. Total influenza A viruses subtyped as H1N1 (*n*=5984), and number of oseltamivir-resistant and oseltamivir-susceptible H1N1 viruses for which oseltamivir susceptibility was determined (*n*=2949), by week, Europe, winter 2007–08. Reproduced from Meijer *et al.*[69] with permission.

America (36% of 275 isolates tested).[70] In Australia, oseltamivir-susceptible H3N2 and B viruses were more common.

In the 2008–09 northern hemisphere season, oseltamivir-susceptible H3N2 viruses predominated in Europe, despite the persistence of the oseltamivir-resistant H1N1 virus.[71] In the USA, however, H1N1 was the predominant influenza A strain, and the majority of the circulating influenza viruses were resistant to oseltamivir (~60%).[71,72] In line with this, the IDSA recommended the use of oseltamivir or zanamivir for treatment or prophylaxis of H3N2 strains, but zanamivir or an adamantane for H1N1; where the subtype is unknown, combining oseltamivir with an adamantane may be considered.[13] It should be noted, however, that since the emergence of pandemic (H1N1) 2009 influenza, the oseltamivir-susceptible pandemic H1N1 virus now dominates over the seasonal H1N1 virus in many countries.[73]

National and regional surveillance data have provided more information on the emergence of A/H1N1-H275Y viruses, showing that, in general, clinical features of infection are similar to those of wild-type virus. Patients in the Netherlands (from whom 28% of 119 H1N1 isolates were resistant),[74] France (366 patients with resistant and susceptible virus)[75] and Norway (265 patients)[76] showed no differences in demographics or outcomes (including hospitalization for the latter) compared with persons infected with susceptible viruses. Equally, in the USA, data from 99 oseltamivir-resistant and 182 oseltamivir-susceptible cases from the 2007–08 season did not reveal any significant differences in terms of demographic characteristics, underlying medical illness or clinical symptoms.[77] A preliminary analysis of 1184 H1N1 isolates across the whole of Europe from the VIRGIL database (43% of all those tested) also found no difference in age group distribution between the resistant and susceptible strains.[78] Notably, the Dutch, Norwegian and American surveillance also found that continued transmission of the mutant viruses was not selected by oseltamivir use,[74,76,77] an observation that was supported by a pan-European study that compared oseltamivir prescription rates and national proportions of resistant viruses, and found no association between the two.[79]

A Danish group reported the death from pneumonia of an 8-year-old boy with A/H1N1 carrying the H275Y mutation (and amino acid substitutions in other proteins),[80] and the death from leukaemia of a 67-year-old Dutch patient infected with a resistant H1N1 strain mutation (H275Y) was also recently documented.[81] Further information from the Netherlands was provided by a case series of two stem cell transplant recipients and an elderly patient who developed influenza infection following exposure to an index patient with community-acquired H275Y-mutated H1N1.[82] In the latter case, transmission of resistant virus was confirmed, and the elderly patient and one of the transplant patients died. Deaths in influenza patients are not uncommon, and some age groups, notably very young children and adults >65 years, have a higher mortality risk than the general population;[83,84] the impaired immune function of the patient with leukaemia and the stem cell transplant recipient may have increased their risk further. New studies are under way to assess the benefit of oseltamivir treatment and prevention in immunocompromised patients (see below).

Safety

Neuropsychiatric adverse events (NPAEs)

From the 2004–05 season, an increased incidence of NPAEs in influenza patients taking oseltamivir was noted through post-marketing surveillance.[85] Analysis of the Roche safety database revealed 3051 spontaneously reported NPAEs in 2466 patients who received oseltamivir between 1999 and 15 September 2007, during which time oseltamivir had been prescribed to ~48 million people worldwide (Roche, data on file). The majority (90.9%) of the reported NPAEs originated in Japan.[85] In both Japan and the USA, higher crude reporting rates were seen in children and young adolescents aged ≤16 years (9.9 and 1.9 events/100000 prescriptions, respectively) than adults (2.8 and 0.8 events/100000 prescriptions). NPAEs were more commonly reported in children (2218 events in 1808 aged ≤16 years

versus 833 in 658 adults) and generally occurred within 48 h of the onset of influenza illness and initiation of treatment.[85]

Roche conducted a comprehensive safety analysis to investigate the increased reporting of NPAEs. In Phase III treatment studies, there was no difference in reporting rates between oseltamivir and placebo (both <1%).[85] Analyses of US healthcare claims databases showed that the risk of NPAEs in oseltamivir-treated patients (n=159 386) was no higher than for those not on antiviral medication (n=159 386), while medical records in the UK General Practice Research Database showed that the relative adjusted risk of NPAEs in influenza patients was significantly higher (1.75-fold) than in the general population.[85] Further US healthcare database analyses have been published since the Roche review and confirm these observations in both the general population aged ≥1 year[86] and those aged 1–17 years[86] and 1–21 years.[87] A literature review revealed that NPAEs have been reported in Japanese and Taiwanese children with influenza before initiation of oseltamivir treatment; events occurring before treatment were similar to those occurring afterwards.[85] A similar observation was also made in a more recent Taiwanese clinical case series.[88]

The *in vitro* and *in vivo* CNS tolerability profile of oseltamivir has been revisited as part of the comprehensive safety review. No clinically relevant differences in plasma pharmacokinetics of
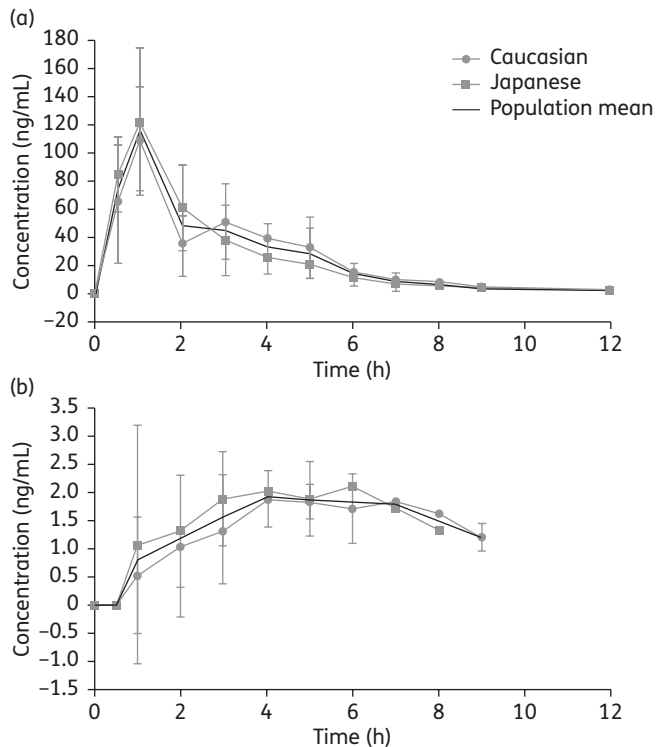
Figure 4. (a) Mean (±SD) concentration–time profile for oseltamivir in plasma after a single oral dose of 150 mg of oseltamivir phosphate in Caucasian (n=4) and Japanese (n=4) subjects and the overall population (n=8). (b) Mean (±SD) concentration–time profile for oseltamivir in CSF after a single oral dose of 150 mg of oseltamivir phosphate in Caucasian (n=4) and Japanese (n=4) subjects and the overall population (n=8). Reproduced from Jhee *et al.*[91] with permission.
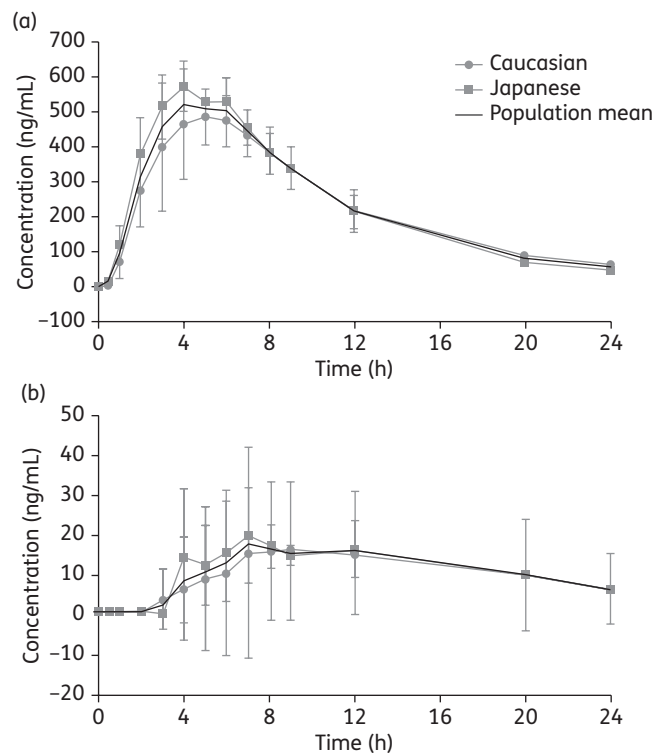
Figure 5. (a) Mean (±SD) concentration–time profile for oseltamivir carboxylate in plasma after a single oral dose of 150 mg of oseltamivir phosphate in Caucasian (n=4) and Japanese (n=4) subjects and the overall population (n=8). (b) Mean (±SD) concentration–time profile for oseltamivir carboxylate in CSF after a single oral dose of 150 mg of oseltamivir phosphate in Caucasian (n=4) and Japanese (n=4) subjects and the overall population (n=8). Reproduced from Jhee *et al.*[91] with permission.

oseltamivir and its active metabolite oseltamivir carboxylate (OC) were noted between Japanese and Caucasian adults[89] or children.[90] Penetration into the CNS of both oseltamivir and OC was low in Japanese and Caucasian adults (CSF/plasma maximum concentration and AUC ratios of ~0.03; Figures 4 and 5),[91] and the capacity for converting oseltamivir into OC in rat and human brain was low.[85] In animal autoradiography studies, brain/plasma radioactivity ratios were generally 20% or lower, and animal studies showed no specific CNS/behavioural effects after administration of doses corresponding to ≥100 times the clinical dose.[85] Oseltamivir and OC did not interact with human neuraminidase or with 155 known molecular targets in radioligand binding and functional assays. A literature review of functional variations of genes relevant to oseltamivir pharmacokinetics and pharmacodynamics and simulated gene knock-out scenarios have not identified any plausible genetic explanations for the observed NPAEs.[85] A literature review indicated that influenza itself may be associated with a variety of neurological sequelae.[92] Based on this information and the findings of the safety review, a disease-mediated pathogenesis for the observed NPAEs appears likely. Recently published retrospective studies have confirmed a lack of association between oseltamivir and NPAEs.

General safety: treatment

Pooled safety data from the oseltamivir clinical treatment programme have been reported at length previously.[93] In adults and children, oseltamivir treatment was generally well tolerated, with an overall incidence of adverse events similar to placebo. In treatment studies in adults, only nausea and vomiting were reported with a higher frequency in the oseltamivir arms, and these events generally occurred on the first or second day, were mild in intensity and resolved without discontinuation. The incidence of adverse events was similar between oseltamivir and placebo and was similar in younger (<65 years) and elderly adults (≥65 years).[93] Limited data in immunocompromised patients also suggest that oseltamivir treatment is well tolerated.[31] In view of the known association between influenza and deaths from cardiac disorders, a thorough review of the available data on cardiac safety in patients exposed to oseltamivir was conducted.[93] No effect on QTc intervals or T wave morphology was evident, and pre-clinical studies showed that oseltamivir had no potential for effects on cardiac repolarization.

In children, vomiting and abdominal pain were the only events that occurred more frequently with oseltamivir; generally, these took place at the start of treatment and resolved rapidly without leading to complications such as dehydration. In the pooled analysis, approximately half of those ≥6 years had asthma.[93] Oseltamivir had no adverse effects on pulmonary function in these children. Similarly, in the treatment study of asthmatic children described earlier, the overall incidence of adverse events was similar in the oseltamivir and placebo arms, with gastrointestinal disorders the most frequently reported events.[20] Vomiting and abdominal pain were slightly more frequent in the oseltamivir group than the placebo group (15.9% versus 11.0% and 6.5% versus 4.3%, respectively), while diarrhoea and nausea were more common with placebo (7.3% versus 5.9% and 4.9% versus 2.4%, respectively).

General safety: prophylaxis

Oseltamivir has a well-established safety profile when used as prophylaxis for varying durations in an array of patient groups. In the 10 day household PEP study reported by Hayden et al.,[44] the most frequently reported adverse events among contacts receiving oseltamivir once daily as PEP were nasal congestion (11%) and nausea (8.3%), while the incidence of vomiting was greater among contacts receiving twice-daily treatment (9.8% versus 4.5% in those receiving PEP). In general, adverse events occurred more frequently in the oseltamivir PEP arm (45.4%) than the treatment arm (30.4% of index cases, 31.4% of contacts), which may reflect the extended duration of therapy (10 versus 5 days).[44] Six weeks of oseltamivir prophylaxis was also well tolerated by adults[45] and elderly nursing home residents,[46] with an adverse event profile similar to placebo. Oseltamivir was also generally well tolerated in the non-randomized paediatric seasonal prophylaxis study by Reisinger et al.[47] Over the 42 day treatment period, 35% of participants reported adverse events, most commonly gastrointestinal disorders, infections and respiratory disorders. No serious adverse events were reported.

A single published report has described the safety and tolerability of oseltamivir as prevention in immunocompromised subjects.[94] Forty-five individuals aged 11–73 years who were resident at a facility for patients undergoing HSCT received oseltamivir PEP following an influenza outbreak; this cohort was matched with another patient group who did not receive prophylaxis (n=45). Oseltamivir was well tolerated compared with controls, and no deaths occurred that were attributable to oseltamivir.

Adverse events and populations of special interest

In a retrospective study of 771 evaluable Japanese infants aged <1 year, the incidence of adverse drug reactions and adverse events was low (3.2% and 5.3%, respectively), with diarrhoea the most frequently reported event (Roche, data on file). No serious adverse drug reactions were recorded. In the previously described study of infants by Tamura et al.,[21] the only adverse event of note in the <1 year group was diarrhoea, which occurred in 1 infant only (2.1%), while in the older treatment group (aged 1–15 years) adverse events were seen in 41 children (8.4%). No serious complications were associated with oseltamivir in either treatment group. In the retrospective analysis by Skopnik and Siedler,[22] all but one of the 157 infants completed the full 5 day course of oseltamivir therapy. Oseltamivir was generally well tolerated, apart from mild gastrointestinal side effects that did not require medication (vomiting in 62 infants and diarrhoea in 34). In at least 10 cases, these symptoms were attributable to concomitant gastrointestinal infections.

Ongoing studies of oseltamivir in seasonal influenza

A prospective, age-stratified, pharmacokinetic, pharmacodynamic and safety evaluation of oseltamivir in children aged <24 months with confirmed influenza is currently being undertaken in collaboration with the US NIH. Additionally, Roche is sponsoring a resistance study [the Influenza Resistance Information Study (IRIS)] that is planned to run for at least three influenza seasons (from 2008–09 to 2010–11) and recruit patients from countries in the northern and southern hemispheres. The study's main objective is to assess the clinical impact of resistance to antiviral drugs, both naturally occurring and drug induced. To achieve this, clinical as well as virological data on susceptible and resistant influenza infections will be collected. The aim is to recruit 1200 influenza patients each year from Europe, the USA, Asia and Australia, and to monitor clinical and virological outcomes in treated and untreated patients with influenza.

Conclusions

The burden of influenza in low- and high-risk groups warrants effective countermeasures. Vaccination is central to disease prevention, but limitations in terms of coverage and efficacy mean effective antiviral options are also important, especially for those at high risk of influenza-associated complications. Oseltamivir is a widely used oral antiviral that is effective and well tolerated in a variety of low- and high-risk patient populations, when used for the treatment and prophylaxis of influenza. There is now a substantial body of clinical and epidemiological evidence to show that oseltamivir therapy reduces the incidence of potentially serious secondary complications. The issue of viral

resistance to oseltamivir remains important, particularly in light of recent increases in the prevalence of resistant strains; ongoing surveillance is essential.

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Transparency declarations

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