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Early administration of oral oseltamivir increases the benefits of influenza treatment

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Our objective was to evaluate the benefit of early treatment of influenza illness using oral oseltamivir. This open-label, multicentre international study investigated the relationship between the interval from illness onset to first dose (time-to-treatment) and illness duration in the intent-to-treat infected population using accelerated failure time (AFT) modelling. A total of 1426 patients (12–70 years) presenting within 48 h of the onset of influenza symptoms were treated with oseltamivir 75 mg twice a day for 5 days during the 1999–2000 influenza season; 958 (67%) had laboratory-confirmed influenza virus infection. Earlier intervention was associated with shorter illness duration ($P < 0.0001$). Initiation of therapy within the first 12 h after fever onset reduced the total median illness duration by 74.6 h (3.1 days; 41%) more than intervention at 48 h. Intermediate interventions reduced the illness proportionately compared with 48 h. In addition, the earlier administration of oseltamivir further reduced the duration of fever, severity of symptoms and the times to return to baseline activity and health scores. Oseltamivir was well tolerated. The most common adverse events were nausea and vomiting, which were transient and generally occurred only with first dosing. When oseltamivir was taken with food, the tolerability was enhanced. The overall discontinuation rate was low (1.8%). In conclusion, the IMPACT study demonstrated that earlier initiation of oral oseltamivir therapy increased its therapeutic effects, which were seen at every time point of intervention and were progressive. Thus, early presentation, diagnosis and treatment of patients with influenza maximized the benefits of oseltamivir therapy.

Keywords: influenza, neuraminidase inhibitors, oseltamivir, treatment

Introduction

Annual influenza outbreaks lasting for 6–8 weeks result in illness in an average of 10% of the population.[1] Influenza disrupts the normal activities of individuals and, because of the large number of people incapacitated by the illness, results in a considerable burden to society.[2,3] Increases of up to five-fold in consultations for influenza-like illness in general practice intensifies pressure on primary healthcare services.[4]

There is a need for effective and well-tolerated treatments that can reduce the impact of influenza on the individual and society. Oseltamivir is the oral prodrug of oseltamivir carboxylate, a potent inhibitor of influenza A and B viral neuraminidase. Oseltamivir is well tolerated and effective for the treatment of acute influenza in previously healthy adults.[5,6] In influenza-infected patients treated within 36 h of symptom onset, oseltamivir reduced the duration of clinical illness by 30% ($P < 0.001$), when compared with symptomatic treatment alone.[5]

The pathogenesis of influenza illness suggests that inhibiting viral replication as early as possible after infection will reduce the duration and intensity of symptoms. In the study of

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Nicholson *et al*.,[6] patients starting oseltamivir within 24 h of symptom onset had a 37% reduction in illness duration compared with placebo. Studies with the inhaled influenza neuraminidase inhibitor zanamivir have also suggested the additional benefit of earlier treatment.[7,8] These findings are consistent with increased treatment benefits that result from early antiviral treatment of other viral diseases.[9,10]

The IMPACT (IMmediate Possibility to ACcess oseltamivir Treatment) study investigated the relationship between the time to intervention and duration of illness as a primary endpoint, plus other parameters of illness, by treating with oral oseltamivir as early as possible after the onset of influenza symptoms.

Materials and methods

This was a prospective, open-label, exploratory, multicentre international study conducted during the influenza season 1999–2000. During local influenza outbreaks, subjects aged ≥13–70 years presenting within 48 h of the sudden onset of fever (≥37.8°C, ≥100°F) with at least two of the following symptoms: cough, sore throat, coryza, myalgia, headache, fatigue and chills/sweats were enrolled and received oral oseltamivir 75 mg twice a day for 5 days. Volunteers were advised to take the study medication with a meal or snack, and ingestion of the first dose was observed directly and the time recorded. Those with uncontrolled chronic medical disorders were excluded as were women who were pregnant, lactating or not using a reliable method of contraception. Individuals who had HIV infection, a transplant or a clinically relevant history of abuse of alcohol or other drugs were excluded. Subjects who had experienced an acute upper respiratory tract infection (URTI), otitis media, bronchitis or sinusitis or who had been treated with an antiviral drug, systemic steroids or immunosuppressants within 2 weeks of the study start were also excluded. Influenza infection was confirmed by virus recovery from nose or throat swabs taken pre-dose and on day 3 (in selected centres only), and/or a ≥four-fold rise in serum antibody titres to influenza virus. Nose and throat swabs were transported to country-specific virology laboratories either in chilled viral transport medium within 72 h or in ambient conditions within 24 h of collection from the patient. The swabs were eluted and inoculated onto Madin–Darby canine kidney (MDCK) cell monolayers and incubated for up to 7 days. Cell-associated influenza A or B viruses were identified using immunofluorescent antibody techniques or the haemadsorption test.

Baseline and day 21 sera were assayed together by measurement of the haemagglutination-inhibition (HAI) antibody or complement fixation test (CFT) antibody. The following antigens were used for the majority of HAI assays: A/Bayern/7/95 (H1N1), A/Sydney/5/97 (H3N2), B/Yamanashi/66/98; the antigens used for CFTs were influenza A and B nucleocapsid.

Temperature and symptom scores were recorded twice daily and a health scale questionnaire was answered daily for 21 days after the start of the study.

The primary endpoint was duration of illness as a function of time to the first treatment dose, calculated from the time of onset of fever (defined as the earliest time that the patient either measured an elevated temperature or felt feverish) in the laboratory-confirmed, influenza virus-infected population. The duration of illness was defined as the time from symptom onset to alleviation of all symptoms. Duration of illness was measured from the onset of fever or when the patient felt feverish until all symptoms were scored as mild or absent and remained so for at least 24 h. Other endpoints included the severity of the influenza illness by measurement of area under the curve of total symptom scores, the times to resolution of fever (assessed as the time to return to an afebrile state, i.e. a temperature of ≤37.2°C), and return to baseline health and activity scores. Adverse events were recorded up to study day 21 (±4) and graded on a four-point scale (mild, moderate, severe, life threatening).

The study was conducted in accordance with the principles of the Declaration of Helsinki (amended) or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The protocols were approved by local or regional ethics committees prior to implementation and all participants gave written informed consent before enrolment.

Analysis of data

To determine the added value of early intervention, the relationship between time to treatment and illness duration from fever onset was analysed. The results were compared descriptively by time-to-treatment groups and also by accelerated failure time (AFT) modelling on the actual data collected.[11] The LIFEREG procedure in SAS (version 6.12) was used to perform the AFT analysis, in a Unix environment. Estimates were produced on the natural log scale, but were back-transformed for presentation in all summary tables. The error structure was modelled using the log-normal distribution, and for all best fit models, normal probability plots of the residuals were produced and examined for indications of lack-of-fit.

The median times of illness duration from illness onset are also presented for time-to-treatment groups together with 95% confidence intervals.

Kaplan–Meier curves of the duration of illness data were constructed for each time-to-treatment group in order to estimate the median duration of illness and associated 95% confidence interval along with other summary statistics.

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Table 1. Summary of the demographics of the safety population

	Oseltamivir 75 mg twice a day ($n = 1426$)
Female, *n* (%)	716 (50%)
Median age (range; years)	40.0 (12–70)
Influenza virus infected, *n* (%)	958 (67%)
type A	944 (66%)
type B	6 (0%)
type A and B	8 (1%)
unknown	26 (2%)
Influenza vaccinated, *n* (%)	121 (8%)

Results

A total of 1428 patients entered the study. Of these, 1426 received study treatment and comprise the intent-to-treat (ITT) safety population (Table 1). Two 12-year-old patients, who deviated from the age inclusion criteria, were included in the ITT population. The intent-to-treat infected (ITTI) population consisted of the 958 (67%) subjects with laboratory-confirmed influenza, 955 of whom received study medication and provided data permitting calculation of the clinical endpoints. There were no major differences in infection rates between the time windows. Of the ITTI population, 140 (15%) subjects entered the study within 6 h of symptom onset, 240 (25%) within the first 12 h and 573 (60%) within 24 h.

There was a correlation between the time of intervention after symptom onset and the illness duration, such that the duration of illness was shorter the earlier treatment began (Table 2). AFT modelling of the data confirmed that earlier intervention was strongly associated with shorter illness duration ($P < 0.0001$) (Table 3 and Figure 1). Intervention within the first 12 h after fever onset reduced the median illness duration by 3.1 days more than if intervention was delayed until 48 h (Figure 2). For every 6 h earlier that oseltamivir was initiated, the predicted median illness duration was shortened by an acceleration factor of 1.09 (8%). This corresponded to a benefit of ~10 h (range 8–15) shorter duration of illness for every 6 h earlier that treatment was initiated. The outcomes based on the absolute time-to-treatment group data and those produced by the use of AFT modelling results were highly comparable.

As well as the additional benefit of early administration on illness duration, benefits were also seen in other efficacy endpoints. Earlier intervention was strongly associated with a shorter time to return to normal health ($P = 0.0001$) and baseline activity ($P = 0.0001$) (Figure 4). Earlier intervention also reduced the fever duration ($P = 0.0115$) (Figure 4) and severity of illness ($P = 0.0023$) (Figure 3). The acceleration factors for these parameters were 1.05, 1.07, 1.12 and 1.03, respectively. Approximately 90% of all influenza-infected

Table 2. Duration of illness observed in the intent-to-treat infected population ($n = 955$) per time-to-treatment group in patients treated with oseltamivir 75 mg twice daily for 5 days

	Duration of illness (h) between onset of symptoms and treatment start				
	0–6 ($n = 140$)	>6–12 ($n = 100$)	>12–24 ($n = 332$)	>24–36 ($n = 258$)	>36–48 ($n = 125$)
Median duration (h)[a] (95% CI)	81.8 (70.7–105.5)	110.2 (93.0–123.5)	111.1 (98.5–122)	127.8 (111.8–151.5)	180.0 (146.7–202.8)

[a]The time from the start of the illness to alleviation of all symptoms.

Table 3. Duration of illness predicted by the AFT model[a] in patients treated with oseltamivir 75 mg twice daily for 5 days

	Time (h) from start of illness to treatment					
	0	6	12	24	36	48
Predicted median illness duration (h)	90.7	98.9	108	128.7	153.3	182.6
Reduction in illness duration (h)[b] (95% CI)	91.9 (78.4–107.7)	83.6 (72.2–96.8)	74.6 (65.0–85.6)	53.9 (47.2–61.5)	29.3 (25.3–33.9)	NA
Acceleration factor[b]	2.01	1.85	1.69	1.42	1.19	NA

[a]Model contains sex, age, baseline total symptom score, vaccination status time-to-treatment, baseline total symptom score time-to-treatment interactions.
[b]Compared with initiation of therapy at 48 h after start of illness.
NA, not applicable; CI, confidence interval.

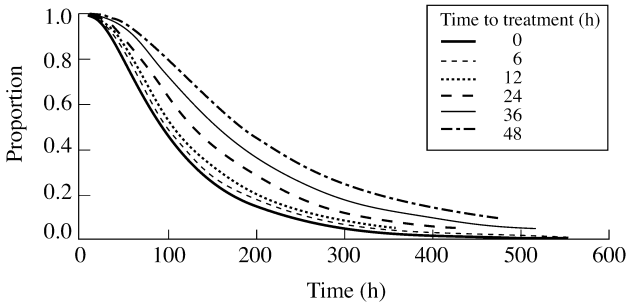

Figure 1. The duration of influenza illness is shorter the earlier that oseltamivir treatment 75 mg twice a day for 5 days is initiated (intent-to-treat infected population).

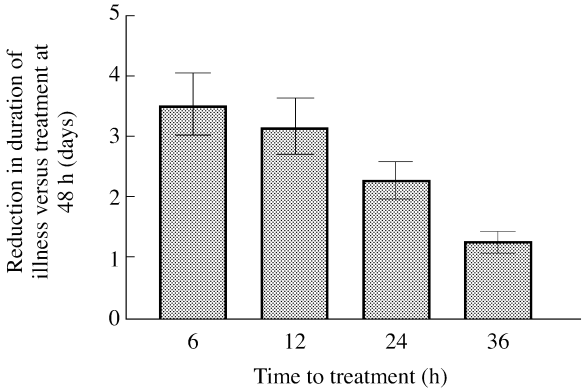

Figure 2. The reduction in days of illness duration with earlier treatment with oseltamivir 75 mg twice a day in comparison with delayed treatment at 48 h (intent-to-treat infected population). The data are median and 95% CI.

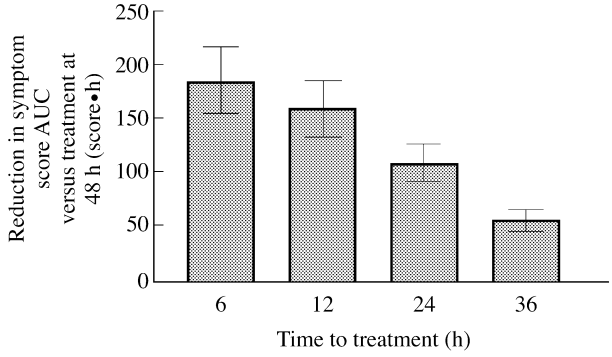

Figure 3. The reduction in total symptom score AUC with earlier treatment with oseltamivir 75 mg twice a day in comparison with delayed treatment at 48 h. The data are median and 95% CI.

patients treated with oseltamivir had a reduction of fever, <37.8°C, within 36 h of taking their first dose.

The duration of illness was seemingly shorter when intervention occurred earlier in patients who were not infected with influenza and treated with oseltamivir, but this was not statistically significant ($P = 0.3783$) (Table 4). Thus, no therapeutic benefit was demonstrable as a result of oseltamivir treatment in non-influenza virus-infected patients.

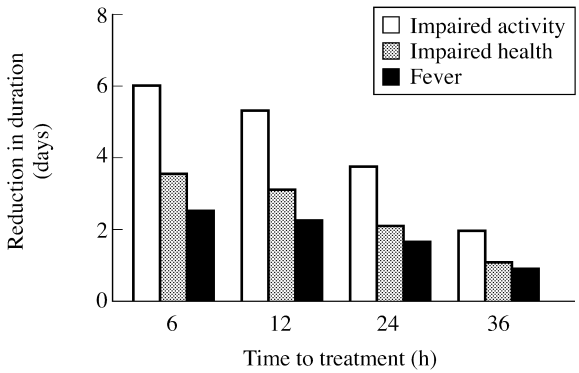

Figure 4. The median reduction in days of impaired activity and health and duration of fever with earlier treatment with oseltamivir 75 mg twice a day in comparison with delayed treatment at 48 h (intent-to-treat infected population).

Oseltamivir was well tolerated. The incidence of adverse event-related drug withdrawal was low, 25/1426 (1.8%), and was similar to the number of patients who withdrew for non-safety reasons (n = 21/1426, 1%). Most adverse events were mild or moderate in severity. The most common adverse events were gastrointestinal, mainly nausea (194/1426, 13.6%) and vomiting (160/1426, 11.2%), which resolved with continued dosing; only 12 subjects (<1%) withdrew as a consequence of these effects. The majority of these events occurred between the first and second dose (~70%). The incidence of nausea was further reduced when the first dose was taken with food (8.6%) compared with no food (13.6%, $P = 0.009$). The overall incidence of vomiting was higher in patients with influenza infection (9.9%) than in those without (6%, $P = 0.012$).

Discussion

The IMPACT study, designed to investigate the relationship of time-to-treatment with the illness duration and other efficacy parameters, has confirmed that greater and incremental benefits can be gained from treating influenza as soon as possible after the appearance of symptoms. The study design was predicated on knowledge that influenza illness is associated with virus replication in the respiratory tract that peaks 24–72 h after illness onset.[12] Thus, drugs like oseltamivir that would ameliorate illness solely by inhibiting virus replication must be administered in the first 48–72 h of illness, and preferably as early as possible. Early intervention was shown to be strongly associated with a shorter duration and a reduced severity of illness, a faster resolution of fever and a faster return to normal health and activity. For the primary endpoint, the data demonstrated that the total duration of illness could be halved if influenza patients were treated early compared with intervention at 48 h. These data complement the results from an earlier study with oseltamivir in which subjects who started active treatment within 24 h of

Table 4. Duration of illness observed in the population without laboratory-confirmed influenza ($n = 461$) treated with oseltamivir 75 mg twice daily for 5 days per time-to-treatment group

	Duration of illness (h) between onset of symptoms and treatment start				
	0–6 ($n = 99$)	>6–12 ($n = 70$)	>12–24 ($n = 167$)	>24–36 ($n = 93$)	>36–48 ($n = 32$)
Median duration (h) (95% CI)	83.0 (75.5–107.0)	77.4 (64.8–105.3)	112.1 (97.0–133.9)	124.5 (115.5–152.0)	196.0 (133.8–250.8)

CI, confidence interval.

symptom onset had a 37% reduction in illness duration compared with 25% in those who initiated therapy within 36 h after onset of illness.[6]

This is the first report to describe the mathematical relationship between illness duration and time to effective antiviral intervention. The results based on the observed time-to-treatment group data and those produced by AFT modelling were highly comparable. The time-to-treatment group data consisted of results for all subjects recruited within specified mean 6 or 12 h windows, whereas AFT modelling permitted us to predict the effect of intervention at any time as well as the results of extrapolation to the limits of time studied. The observed effects and the values predicted by AFT modelling were somewhat different even though they were both derived from analysis of the study database.

The absence of a concurrent control group treated with placebo in this study might raise the question of whether the beneficial effects of early initiation of oseltamivir plus symptomatic therapy in persons with influenza illness were due to early initiation of symptomatic therapy alone. This is unlikely given the previous observation in persons with laboratory-confirmed influenza who were treated with the same symptomatic therapy plus placebo,[6] in whom no difference was observed in the median duration of illness between those persons treated at <36 h and those in whom therapy was initiated within 24 h of illness onset.

The study confirmed that physicians can accurately diagnose influenza in patients reporting soon after fever onset by use of a clinical case definition and knowledge that influenza virus is circulating within the community. There were no major differences in the sensitivity of the clinical diagnosis between the treatment time windows, and the 67% infection rate was similar to that found in previous placebo-controlled treatment studies with oseltamivir.[5,6] The study also confirmed that influenza presents with characteristic sudden identifiable and severe symptom onset,[13] only 2/958 patients having presented with mild symptoms in this study. Education of potential volunteers about symptoms of influenza illness made possible self-referral for diagnosis and the implementation of antiviral therapy.

The proportion of individuals with influenza who receive some form of drug treatment is 59%. Antibiotics are the most frequently prescribed drugs (45%), followed by antipyretics/analgesics (22.5%).[3] Antibiotics are likely to be prescribed to patients with influenza in all age groups.[14,15] Inappropriate antibiotic treatment provides no medical benefit and increases the risk of antibacterial resistance.[15] The results of this study confirm that oseltamivir therapy would be more logical than antibiotics for patients with uncomplicated influenza.

Translating the results of this study into clinical practice will be challenging, but, it is argued, clinically important. Strategies to do so must provide early diagnosis and access to oseltamivir therapy without markedly increasing the workload for practitioners in the influenza season. This study has demonstrated that early presentation is possible by public education of influenza symptom characteristics, as approximately two-thirds of those who were infected presented to their general practitioners within 24 h of symptom onset, and a quarter within 12 h. One solution may lie in application of the UK Department of Health guidelines to implement the NICE recommendations for another neuraminidase inhibitor drug, zanamivir.[16] Telephone triage and walk-in centres for specific patient groups organized by practice nurses or other health professionals, e.g. community pharmacists, working to a protocol of standard diagnostic questions will help address the issues of overburdened GPs and facilitate timely initiation of treatment.

The overall incidence and pattern of adverse events were similar to those reported in previous studies.[5,6] Nausea was significantly reduced by taking the first dose of oseltamivir with food, suggesting that the mechanism of action may be at the local gastric level. The proportion of patients who discontinued drug because of gastrointestinal events was small and similar to previous studies, due to the fact that the majority of these events were of isolated occurrence after the first dose and did not persist with continued dosing.

Conclusion

The IMPACT study adds to our understanding of the benefits of oral oseltamivir therapy of influenza, by demonstrating that earlier intervention enhances treatment effects. Early intervention can reduce the total illness duration by up to one

half compared with later treatment, resulting in faster recovery and resumption of normal activities. The IMPACT study demonstrated the value of early presentation, and diagnosis of patients with influenza illness and their treatment with oseltamivir.

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