Early versus late oseltamivir treatment in severely ill patients with 2009 pandemic influenza A (H1N1): speed is life

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The need for early antimicrobial therapy is well established for life-threatening bacterial and fungal infections including meningitis and sepsis/septic shock. However, a link between the outcome of serious viral infections and delays in antiviral therapy is not as well recognized. Recently, with the occurrence of the influenza A/H1N1 pandemic of 2009, a large body of data regarding this issue has become available. Studies analysing data from this pandemic have consistently shown that delays in initiation of antiviral therapy following symptom onset are significantly associated with disease severity and death. Optimal survival and minimal disease severity appear to result when antivirals are started as soon as possible after symptom onset.

Keywords: antivirals, outcome, virus, critical care, therapy

Introduction

Although clinicians have been aware of the need for rapid antimicrobial therapy for optimal outcomes in certain bacterial infections for >30 years, only now is a potential basis for that relationship becoming apparent. An emerging body of literature suggests that the speed with which a pathogen is eradicated is the central driver of outcome in life-threatening infections in the critically ill.3,4 This link has been firmly established for bacterial meningitis.3,4 However, a relationship between survival and rapidity of initiation of antimicrobial therapy for serious bacterial infections other than meningitis has also been demonstrated in recent years. For example, Meehan et al.5 showed that the outcome of community-acquired pneumonia is linked to the speed of initiation of appropriate antibiotic therapy. Similarly, a relationship between outcome and delays of therapy has also been shown to exist with bacteraemia, fungaemia and nosocomial pneumonia.6–11 A very strong link between the speed of antimicrobial initiation, bacterial clearance and outcome has been shown to apply in septic shock in animals12 and humans.13 In this regard, the simple maxim ‘speed is life’ clearly applies in the clinical management of these conditions.

A connection between the outcome of serious viral infections and delays in therapy is not as well established. Nonetheless, data that can be used to infer such a relationship does exist. Faster clearance of hepatitis C virus in response to interferon-α therapy is associated with improved clinical outcomes,14 with larger doses of interferon being more effective than smaller doses.15,16 Similarly, more rapid clearance of herpes simplex virus (HSV) DNA as measured by PCR has been associated with improved outcomes in herpes encephalitis.17 Since rapid clearance of pathogens is likely the central determinant of outcome in any infection where there is a time-dependent risk of irreversible and irreplaceable organ injury, a relationship between early antiviral therapy and survival can be anticipated in life-threatening viral infections, including influenza.

Randomized controlled trials of mild influenza infection

Oseltamivir, a licensed oral agent that selectively targets influenza virus neuraminidase, has been shown to inhibit viral replication in animal models and in human disease.18 Other neuraminidase inhibitors exhibit similar activity. Several randomized controlled studies of oseltamivir have been performed in ambulatory subjects with spontaneous or experimentally induced influenza infection. In the study by Hayden et al.19 of experimental influenza B infection in 235 subjects, oseltamivir therapy at either 75 or 150 mg orally twice daily for 5 days resulted in a 4-fold reduction in median viral shedding duration from 4 days to 1 day. There was no difference based on the dose of oseltamivir administered. Treanor et al.20 studied 629 subjects with mild influenza A infection; patients were randomized to either placebo, oseltamivir 75 mg orally twice daily or 150 mg orally twice daily, each for 5 days. Both doses of oseltamivir therapy reduced the duration of illness, severity of illness, duration of fever and incidence of secondary complications.
observed compared with placebo. In another study by Nicholson et al.,\textsuperscript{21} involving 726 adults with naturally occurring laboratory-confirmed influenza, oseltamivir therapy reduced both viral shedding and duration of symptoms (by 1–1.5 days) with similar risk of nausea and vomiting in both dosing arms. Falagas et al.\textsuperscript{22} demonstrated that complications of influenza are reduced by the use of neuraminidase inhibitors in both low-risk (i.e., otherwise healthy, \(n=2621\)) and high-risk (\(n=475\)) patients in a meta-analysis of 11 randomized controlled trials, 10 of which were double-blind. The beneficial effects were more pronounced in high-risk patients. These studies demonstrate a clear benefit of oseltamivir therapy in mildly ill influenza cases, particularly those at high risk. However, randomized study data on the efficacy of oseltamivir therapy in severely ill patients with influenza have been lacking.

**Observational studies of severe influenza infection**

In the absence of firm data from randomized studies of severely ill patients, clinical knowledge in this area is dependent on observational studies. In one prospective study, McGeer et al.\textsuperscript{23} demonstrated that oseltamivir treatment (even after 48 h admission) improved 15 day survival in 327 adult patients hospitalized with influenza between 2005 and 2007. Similarly, several different Asian studies demonstrated improved survival among hospitalized patients who were treated with oseltamivir. In the first, Lee et al.\textsuperscript{24,25} showed that initiation of oseltamivir within 4 days of onset of influenza-associated symptoms was associated with improved survival in multivariate analysis (\(n=356\)). Treatment with oseltamivir was also strongly associated with survival in multivariate analysis [adjusted hazard ratio for death 0.27; 95% confidence interval (CI) 0.13–0.55, \(P<0.001\)] in an independent follow-up study of seasonal influenza by the same group involving 754 patients (>75% with H3N2 infection).\textsuperscript{26} In another study, Hanshaoworakul et al.\textsuperscript{27} showed that oseltamivir treatment was associated with improved survival (compared with no antiviral treatment) in hospitalized patients with seasonal influenza (approximately one-third of whom had evidence of viral pneumonitis). Recent data also suggest that therapy of severe seasonal influenza A/H1N1 infections requiring intensive care unit (ICU) support yields improved survival.\textsuperscript{28} In addition, early therapy with oseltamivir is associated with improved outcomes with avian A/H5N1 influenza infections, although a beneficial effect of therapy up to 6–8 days following symptom onset was present.\textsuperscript{29} With respect to the 2009 H1N1 pandemic, Dominguez-Cherit et al.\textsuperscript{30} pointed out that patients requiring ICU care who received oseltamivir demonstrated better mortality rates than those who did not. Among 58 of 899 confirmed or suspected patients requiring ICU admission, neuraminidase inhibitor treatment (versus no treatment) was associated with improved survival [odds ratio (OR) 8.5; 95% CI 1.2–62.8].

Other studies performed both before and during the 2009 influenza A/H1N1 pandemic have supported these results. Some of these studies suggest that oseltamivir limits symptom duration, shortens viral shedding and reduces hospital length of stay. Aoki et al.\textsuperscript{31} prospectively studied 1426 patients presenting with seasonal influenza within 48 h of symptom onset. Initiation of oseltamivir was shown to be associated with shorter duration of clinical symptoms, including fever, reduced severity of symptoms and faster return to baseline activity and health scores. A slower clearance of nasopharyngeal influenza viral RNA load has been associated with increased severity of illness in 2009 pandemic H1N1 influenza.\textsuperscript{32} While more rapid clearance is associated with a decreased hospital length of stay in H3N2 and other seasonal influenza.\textsuperscript{25,33} Further, the duration of viral shedding is reduced with earlier initiation of oseltamivir among both seasonal\textsuperscript{24,25,33} and 2009 pandemic isolates.\textsuperscript{34,35} Studies of oseltamivir-susceptible seasonal influenza virus infection have suggested that initiation of oseltamivir within 48 h of the onset of symptoms of influenza is associated with a 1 day reduction in the duration of symptoms in ambulatory patients.\textsuperscript{36} Lee et al.\textsuperscript{25} also showed that initiation of oseltamivir within 48 h of symptom onset in hospitalized patients was associated with a 2 day (from 6 days to 4 days) reduction in hospital length of stay. Further, the duration of fever has been shown to be reduced in 2009 pandemic H1N1 influenza by treatment with oseltamivir.\textsuperscript{35} Available retrospective data also suggest that oseltamivir therapy may reduce the risk of secondary bacterial superinfection and hospitalization.\textsuperscript{37,38}

**Impact of antiviral therapy delay**

In view of the data showing relationships between the speed of pathogen clearance, outcome and use of antiviral/antimicrobial therapy for serious influenza and major bacterial/fungal infections, a potential survival benefit with rapid initiation of anti-influenza therapy in severely ill patients is predictable. Observational studies performed during the recent 2009 H1N1 influenza pandemic have already noted a relationship between early therapy and improved clinical outcome. Jain et al.\textsuperscript{39} described a relationship between time from onset of symptoms to initiation of antiviral therapy (almost exclusively oseltamivir) and outcome. The median delay in therapy initiation among all hospitalized patients was 3 days (range 0–29 days; 39% patients <48 h); among those requiring ICU admission, 7 days (range 0–24 days; 23% <=48 h) and among deaths, 8 days (range 3–20 days; 0% <=48 h). Similarly, Louie et al.\textsuperscript{40} reported that among 60 pregnant women who acquired 2009 pandemic H1N1 influenza, those for whom antiviral therapy was initiated >48 h after symptom onset had a 4-fold increased risk for ICU admission or death. All 8 deaths among the 22 pregnant or early post-partum patients occurred among those who had not received antiviral therapy within 48 h of symptom onset. Similar results were seen with a later, larger \((n=788)\) cohort of pregnant patients collected by the CDC.\textsuperscript{61} Supporting these findings, Zarychanski et al.\textsuperscript{42} have shown that the interval from onset of symptoms to initiation of antiviral therapy among 588 confirmed treated infections was associated with severity of illness as assessed by the incremental management in the community (i.e. without hospital admission), in the hospital setting or in an ICU environment in multivariate analysis. The median interval from onset of symptoms to initiation of antiviral therapy was 2 days [interquartile range (IQR) 1–3 days] for community cases, 4 days (IQR 2–6 days) for patients admitted to hospital and 6 days (IQR 4–9 days) for those admitted to an ICU \((P<0.001)\).
While all these studies suggest that faster initiation of antiviral therapy could be associated with superior clinical outcomes, none attempted to rigorously assess the specific impact of delays in initiation of antiviral therapy by adjusting for potential confounding variables. In this issue of *Journal of Antimicrobial Chemotherapy*, two studies attempt to do that. Rodríguez et al. assessed 657 patients with severe 2009 pandemic influenza A/H1N1 admitted to the ICU in Spain. They divided patients into those receiving antiviral therapy within or after 48 h of symptom onset. In multivariate analysis, early oseltamivir initiation (i.e. <48 h from symptom onset) was associated with an adjusted OR of death of 0.44 (95% CI 0.21–0.87, P = 0.02). Other significant variables included the need for prone ventilation, the number of quadrants involved on chest radiograph and the APACHE II score. A propensity score analysis of the impact of time from symptom onset to antiviral therapy initiation yielded similar results. Hiba et al. examined the impact of early oseltamivir initiation on subsequent development of complications (as defined by development of radiographic pneumonia or severe hypoxia) in 449 hospitalized patients with 2009 pandemic influenza A/H1N1 infection in Israel. Patients who had oseltamivir therapy initiated ≥48 h after symptom onset experienced a significantly higher adjusted risk for complications (OR 2.20, 95% CI 1.47–3.57) than patients who received early therapy. This increased risk persisted after adjusting for the propensity for early therapy.

**Limitations and lessons of study data**

All human studies supporting initiation of early antiviral therapy for severely ill patients with influenza are observational in nature. As such, subjects are not randomized and there is variability in dosing regimens and supportive care. With respect to the studies included in this issue, subjects were selected in requiring admission to the ICU or the hospital. Outpatients are not included in either analysis. All of these are intrinsic limitations to observational studies. In addition, these types of studies are subject to several types of bias. Selection bias is the most obvious. Recognized or unrecognized aspects of the clinical presentation or epidemiologic factors may impact on the decision to start early versus delayed therapy. Although multivariate logistic regression and propensity adjustment can help to address selection bias (as used in the studies published in this issue), unrecognized or unmeasured factors impacting treatment may be overlooked. Another form of bias that can prejudice an observational study is immortal time bias. Immortal time bias occurs when survival duration is linked to an inappropriate reference point yielding an inaccurate time-dependent survival probability. In addition, any retrospective study with a high early mortality risk may also demonstrate a survival duration-related selection bias. Patients who are known to have lived long enough to receive oseltamivir after 48 h of survival from symptom onset may be more likely to live to a given temporal endpoint than the group who are only known to have lived (and received oseltamivir) within 48 h. Contrary to the findings of both studies, these time-related biases would tend to favour better outcomes in the delayed therapy group. Nonetheless, statistical corrections can be used to adjust for such biases. Another way to do this for the studies in this issue would have been to examine only those patients surviving or developing complications after both groups have had a similar opportunity to receive antiviral therapy (e.g. 96 h after symptom onset to include both early and late therapy). In this way, both study groups have a common temporal start point for assessment of death or complications. The disadvantage to this approach is that deaths occurring before the designated ‘start’ point are lost from analysis. Hiba et al. used a similar approach in a subanalysis in which they looked at events occurring only after initiation of antiviral therapy, finding that late oseltamivir was only marginally associated with complications. It is possible that the results described in these studies may be affected, in part, by these biases.

Prospective, randomized controlled trials would be ideal for assessing the question of whether early antiviral therapy improves clinical outcomes in severely ill patients with influenza. However, ethical considerations make this approach appropriately unacceptable. Such a study will likely never be performed.

The studies reviewed do provide lessons for future investigations of severe influenza. These investigations should include comparisons between available antiviral agents such as oseltamivir, zanamivir and peramivir in addition to the impact of adjunctive therapies including corticosteroids and hyperimmune globulin. For observational studies, appropriate robust adjustments for selection and immortal time biases should be prospectively planned and incorporated into any analyses. Where possible, mortality is an ideal endpoint, but the occurrence of serious complications or hospital and ICU lengths of stay may suffice where subject numbers require. Ultimately, randomized, controlled, double-blind trials of the effectiveness of various new antivirals and adjunctive therapies in severely ill hospitalized patients will be necessary in order to provide definitive evidence of optimal therapy.

**Conclusions**

Given the current absence of randomized controlled trials, management guidelines for severe influenza infections requiring hospitalization will continue to necessarily derive from experimental animal influenza studies; randomized, controlled studies of patients with mild influenza; and observational studies of naturally occurring, severe influenza infection. Fortunately, all these data yield a consistent conclusion. Consensus guidelines on pharmacological therapy of severe influenza infection have been recently enumerated in the context of the pandemic 2009 influenza A/H1N1. These guidelines recommend consideration of high-dose (300 versus 150 mg/ day oseltamivir) and prolonged (10 rather than 5 days) neuraminidase inhibitor therapy, but specifically call for initiation of antiviral therapy as quickly as possible after diagnosis of severe influenza infection. Clearly the maxim that applies to antimicrobial management of other life-threatening infections similarly applies to antiviral therapy of severe influenza: speed is life.

**Transparency declarations**

The author’s institution holds funding support on behalf of the author from Astellas, Pfizer, GSK and Roche for investigator-initiated original research.
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