The Beneficial Effects of Neuraminidase Inhibitor Drug Therapy on Severe Patient Outcomes During the 2009–2010 Influenza A Virus Subtype H1N1 Pandemic

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(See the major article by Muthuri et al on pages 553–63.)

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Elsewhere in the pages of the *Journal*, Muthuri et al answer a question of substantial contemporary importance to clinicians and public health decision makers, namely, whether antiviral therapy for influenza can reduce severe outcomes of the disease in hospitalized patients [1]. In a welcome affirmation of the effectiveness of neuraminidase inhibitor (NAI) treatment, they report that a meta-analysis of 90 observational studies involving 34 895 patients of whom 85% had laboratory-confirmed 2009 pandemic influenza A virus subtype H1N1 (A [H1N1]pdm09) infection revealed that antiviral therapy, principally oseltamivir, initiated within 48 hours of symptom onset reduced the likelihood of severe outcomes, namely admission to a critical care unit or death, by 49%–65%. The strength of the conclusions resides both in the methodologic rigor applied to the meta-analysis of the component studies and the large numbers of studies and patients analyzed. This finding confirms earlier reports of reduced mortality with oseltamivir therapy in those hospitalized with seasonal [2] or avian A(H5N1) [3, 4] influenza. The findings in the current report also complement observations from ecologic studies [5]. For example, Japan, the country with highest per capita use of NAIs during the 2009 pandemic, also had the lowest case-fatality rate and remarkably no reported deaths in A(H1N1)pdm09–infected pregnant women [6, 7]. More recently, a country-based analysis found that each 10% increase in oseltamivir supply (calculated in kilograms per 100 000 people) was associated with a 1.6% reduction in A (H1N1)pdm09 mortality [8].

While previous analyses and the current one have generally found greater effects with earlier compared with later therapy, it is important to note that multiple observational reports in those hospitalized with seasonal, A(H1N1)pdm09, or avian A(H5N1) influenza indicate that a treatment benefit can be demonstrated up to 5 days after symptom onset, including studies in high-risk groups such as pregnant women [2–4, 9–11]. It makes sense that even delayed antiviral intervention would benefit patients, when one considers the protracted duration of viral replication in many patients with serious influenza, sometimes despite oseltamivir administration [12, 13], compared with its relatively short duration in outpatient adults with uncomplicated influenza. As pointed out by Muthuri et al, the timing of NAI initiation was examined carefully in only a few studies. Delayed initiation often reflected late diagnosis or presentation to care and belated efforts at salvage. Indeed, during the pandemic, misunderstanding the potential value of therapy initiated beyond 48 hours of illness unfortunately led many clinicians to not administer NAIs to those who might have benefited. Thus, using 48 hours as a threshold for delayed therapy in hospitalized patients covers a diversity of reasons for late onset of therapy and may be less relevant than in outpatient settings. While time to treatment initiation is a key variable in assessing effectiveness, future analyses should also examine illness severity, cause for hospitalization (eg, influenza-associated pneumonia, exacerbations of underlying conditions, and presence of secondary bacterial infections), comorbidities, and virologic markers at the time of initiating therapy, preferably with propensity scoring that takes such factors into consideration.

This current meta-analysis has advanced our understanding of the effectiveness

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of antiviral therapy for the management of pandemic influenza that began during the 1968–1969 global outbreak caused by the influenza A(H3N2) Hong Kong virus 44 years ago. Antiviral therapy with amantadine was then first demonstrated to be more effective than placebo in accelerating the resolution of pandemic illness in otherwise healthy adults [14, 15]. In 1978, during the Russian influenza A/USSR/77(H1N1) pandemic, comparable therapeutic effects of both adamantanes, amantadine and rimantadine, were again demonstrated using a placebo-controlled, randomized trial design [16]. However, the limited usefulness of the adamantane class of drugs for widespread use on a public health scale came to be recognized, given the rapid emergence of resistance during treatment and, in the case of amantadine, a narrow toxic to therapeutic ratio that necessitated individualized prescribing on the basis of renal function and weight, plus careful monitoring during therapy because of side effects. The development of NAI therapy provided clinicians and public health decision makers with treatment options that were less limited by concerns about viral resistance, or, in the case of amantadine, safety. Cumulated evidence on NAI efficacy and safety for treatment of seasonal influenza and uncertainty about the potential severity of disease caused by a new virus precluded the use of the placebo-controlled, randomized study design to test the hypothesis that NAI therapy could favorably impact severe outcomes during the A(H1N1)pdm09 pandemic. Therefore, it fell to analysis of data from multiple observational studies to estimate the effect of NAI therapy on outcomes of the 2009–2010 pandemic, as has been done in the current report.

The limitations of the data and the conclusions drawn from them are thoughtfully discussed by Muthuri et al. For example, their findings of an increased likelihood of pneumonia with NAI use and that NAI treatment versus no preadmission NAI in subsequently hospitalized patients did not significantly reduce mortality highlight the key issue of confounding by indication. As pointed out by the authors and previously by others [11], sicker patients are more likely to receive NAI therapy, and untreated patients are likely to have had milder disease. Thus, comparisons between NAI-treated and untreated patients in the context of these observational studies are fraught with potential confounding and underestimate beneficial drug effects. In addition, one needs to consider the key questions not addressed in this analysis. Because the scope of the studies considered was limited to hospitalized patients, it could not confirm earlier reports from studies of antiviral therapy for seasonal influenza that found early treatment to reduce the risks of influenza-associated complications and hospitalizations [2]. Other key medical and public health outcomes, such as drug tolerability, antiviral resistance emergence and its relationship to effectiveness, the durations of supplemental oxygen therapy, hospital care, transitional facility care, and time to overall functional recovery, and the causes of mortality also remain to be addressed [17]. The current analysis, moreover, did not have sufficient numbers to assess the effectiveness of specific NAIs other than oseltamivir, so it remains unclear whether inhaled drugs such as zanamivir are as safe and efficacious as ingested or injected NAIs in hospitalized patients. Of note, the optimal dose, duration, and even makeup of NAI therapy in hospitalized influenza patients remains uncertain. Available data suggest that more protracted administration is warranted in seriously ill or immunocompromised patients, while other careful studies using sequential sampling of patients given oseltamivir have indicated a need for more robust antiviral effects, especially in those with severe pneumonic disease [12, 13]. Such virologic findings and the occurrence of deaths despite early therapy [18] highlight the importance of developing more potent antiviral regimens for such patients, particularly antiviral combinations. However, evidence indicates that some NAI combinations, particularly oseltamivir plus zanamivir, may result in antagonistic antiviral effects and lesser clinical benefit, reminding clinicians about the need for detailed preclinical studies and special care when moving on to combination antiviral therapy [19, 20]. Hopefully, new data to address some of these issues will come from, in part, the ongoing randomized, controlled trials of intravenous NAIs.

Although the current study provides clinicians and public health decision makers an answer to an important question at the apex of the hierarchy of the therapeutic effects of anti-influenza drug therapy, questions remain whose solution would further advance our ability to strategically use antiviral drugs to improve the management of influenza outbreaks, small and large. Some of these remaining questions include whether antiviral therapy reduces transmission of influenza; whether therapy mitigates disease without reducing the immune responses to infection and, hence, future protection against drift virus variants; whether postexposure prophylaxis has advantages over early initiation of therapy; and which strategies are most effective at reducing risk of antiviral resistance development and transmission.

The current report included studies conducted up to the declaration of the end of pandemic, in August 2010. However, it is important to emphasize that A(H1N1)pdm09 continues to circulate and cause serious illness and mortality. Studies of mortality patterns in past pandemic periods found that individuals aged ≤65 years continued to experience excess mortality for many years after introduction of the pandemic strain [21]. Consequently, wider use of NAI therapy based on the recommendations of Centers for Disease Control and Prevention and the World Health Organization can mitigate these effects. Of

concern, studies have found reversion toward prepandemic prescribing patterns in United States [22] and elsewhere, with the consequence of worsened outcomes.

In closing, the current report included patients treated in 29 different countries, reflecting the global scale of the pandemic and the widespread interest of researchers in the question of the beneficial effects of NAI therapy on patient outcomes. However, all the studies included in the systematic review were observational designs, most were retrospective, and the methods used for data collection and reporting varied, so it is unsurprising that the meta-analysis found considerable heterogeneity across studies and risk of bias in reporting findings. Furthermore, the authors were hampered by the lack of access to individual patient data. Such circumstances highlight the critical need for clinical research networks, both domestic and international, that can collect samples and data in a systematic, prospective manner and conduct randomized trials of interventions. In this regard, a number of international funding organizations recently have supported the formation of the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), a global federation of >30 existing clinical research networks, launched in December 2012 [23]. ISARIC is committed to undertaking pathogenesis and treatment studies both in response to emerging infectious disease events and in severe acute respiratory infections necessitating hospitalization including influenza during the interpandemic period. Such initiatives need to be supported and sustained if we are to develop the key evidence needed to inform clinical management for current and future severe acute respiratory infection and emerging infectious disease threats.

Note

Potential conflicts of interest. F. G. H. has served as an unpaid consultant to multiple companies involved in influenza antiviral development (including Roche, GlaxoSmithKline, Bio-Cryst, Nexbio, Toyama). The University of Virginia received honoraria for his work in the Neuraminidase Inhibitor Susceptibility Network (NISN) from 2008 to 2011; NISN received financial support from Roche and GlaxoSmithKline. F. Y. A. reports no potential conflicts.

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