

***Options for the Control of Influenza VII* Conference Summary
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The VII Options for Influenza Conference brought influenza scientists from around the world together in Hong Kong, 16 months after pandemic H1N1 influenza A virus [pH1N1] was first reported to be the cause of serious illness in two children in California (1) in April 2009 and one month after the World Health Organization [WHO] declared the pandemic over, in August 2010. Not surprisingly, pH1N1 virus and the pandemic itself were centerpieces of discussion at the Conference as were the contributions of antiviral drugs, vaccine, other pharmaceuticals and such non-pharmaceutical interventions as school closures, home quarantine and social distancing [0-872-577]. We summarize here pertinent published data on oseltamivir and zanamivir efficacy and safety plus information presented at the conference on the emergence of antiviral drug resistance, new antiviral drugs, combination treatments, immunomodulators and other agents.

Oseltamivir and zanamivir are efficacious for seasonal and postexposure prophylaxis [PEP] as well as treatment in healthy adults as evidenced in controlled, clinical trials (2). Their ability to prevent lower respiratory tract complications of influenza is considered unclear at this time based on data from controlled trials. However, in at-risk populations of adults, accumulated evidence from observational studies suggests that oseltamivir therapy reduces secondary respiratory complications of influenza including a reduction in in-hospital mortality (3-5). In healthy children, controlled trials demonstrate that these agents shorten the duration of illness and hasten return to normal activity and oseltamivir reduces the incidence of secondary complications in children (6). Both agents are well tolerated: Side effects are limited to nausea [adults] and vomiting [children] which are reversible and generally mild.

Based in part on these data, neuraminidase inhibitors were widely used to treat and prevent pH1N1 influenza in accordance with recommendations of WHO (7) and guidelines such as those from the Centres for Disease Control [CDC] (8). Patients in a wide range of vulnerable and high-risk groups were treated based on the belief that high-risk groups for the development of complications of pH1N1

influenza were likely to be similar to those defined for seasonal influenza. Antiviral therapy appeared to be beneficial: Pregnant women with pH1N1 who were treated with antiviral drugs within two days of illness onset were less likely to require admission to an intensive care unit [ICU] than those who began therapy more than four days after symptom onset [9% vs. 57%; relative risk 6.0; 95% CI 3.5-10.6] (9). Among immunosuppressed solid organ transplant recipients, antiviral treatment, primarily oseltamivir monotherapy given within 48 h of influenza symptom onset, reduced the likelihood of admission to an ICU three-fold, from 27% to 8% (10).

Neuraminidase inhibitor therapy appeared to reduce disease severity and mortality in other patients with pH1N1 illness: Among 10,048 patients with clinically diagnosed influenza, confirmed by laboratory testing as pH1N1 in 46%, 68% were previously healthy individuals with no underlying medical condition (11). They presented to the Emergency Room with early, relatively mild illness of median duration 1 d. Oseltamivir therapy, prescribed for 99.7% of patients, appeared to result in a low impact on the use of hospital beds [2% were hospitalized] and infrequent admission to the ICU [0.1% of patients] with no influenza-associated deaths. Among 272 more seriously ill patients with pH1N1 infection requiring hospitalization for influenza complications [40% pneumonia], 73% had at least one underlying medical condition. Antiviral therapy [94% oseltamivir and 10% zanamivir monotherapy, 6% oseltamivir combined with M2 inhibitors] initiated within two days of illness onset appeared to be significantly associated with a positive outcome, namely, a lesser likelihood of admission to an ICU and low mortality rate (12). In Japan, early treatment of children hospitalized with pH1N1 influenza was similarly reported at the Conference to reduce the severity of illness (13). Of 1000 hospitalized children with laboratory-confirmed pH1N1 influenza, 65% had been hospitalized for pneumonia or bronchitis and 25%, for neurologic complications. Sixty-six percent had no underlying illness. Neuraminidase inhibitors [oseltamivir 80%, zanamivir 18% and peramivir 1% and 1% oseltamivir with zanamivir] were

administered within 48 h of illness onset in 82%. Only 0.9% of patients required mechanical ventilation of whom only one died.

At the Conference new data were presented concerning the potential advantage of using a larger oseltamivir dose to treat patients with serious influenza. In a randomized trial, standard dose oseltamivir [75 mg twice daily] and high dose [150 mg twice daily] treatment of severe influenza in Vietnam, Thailand and Singapore from April 2007 to January 2010, were compared (14). The primary endpoint was sustained cessation of viral shedding at day 5 of treatment. One hundred fifty-two individuals were randomized to standard treatment and 159, to high dose. Seventy-eight percent were children in both groups, which were similar in other characteristics. At enrolment, 16% and 13% required ICU care and 8% and 6%, respectively, mechanical ventilation. Length of illness prior to initiation of therapy was 5 d [median; range 1-10 d] in both groups. At day 5 of therapy, 32% and 30% in the two groups, respectively, were still shedding virus. High dose oseltamivir did not reduce the need for, or duration of, supplemental oxygen nor the need for, or duration of, subsequent admission to the ICU. High dose oseltamivir appeared safe with 14% in both groups having a grade 4 adverse event. It was concluded that high dose oseltamivir was safe but offered no additional benefit over the standard dose regimen in reducing virus shedding at day 5 of treatment. Nonetheless, the value of high dose oseltamivir initiated earlier in the course of illness and its effect on the risk of complications remains unclear.

Oseltamivir and zanamivir are efficacious against seasonal influenza viruses for seasonal and postexposure prophylaxis [PEP] in close contacts (15) as well, probably, in controlling institutional outbreaks (16). There have been published reports of oseltamivir efficacy in preventing pH1N1 illness. Oseltamivir 75 mg/d administered prophylactically for 10 days for control of outbreaks of pH1N1 influenza in four military units in a camp reduced the number of cases from 6.4% to 0.6%. Side effects were primarily gastrointestinal [2.7% nausea or vomiting or diarrhea 1.7%] (17). PEP was effective in

preventing secondary cases of pH1N1 influenza in household contacts of infected children during a school outbreak (18). The secondary household attack rate was reduced to zero from 5.9% in those not given postexposure prophylaxis (18). At the Options meeting, few new data were presented on the efficacy of neuraminidase inhibition in preventing pH1N1 illness. Australian researchers reported on good compliance with strategies involving home quarantine and antiviral prophylaxis to mitigate the pandemic during its early phase (19). Three quarters of individuals prescribed prophylactic oseltamivir stated that they took the full course of apparent postexposure prophylaxis with few side effects. However, the researchers were concerned with selection bias in this retrospective telephone survey. They concluded that much more knowledge is required on antiviral drug acceptability to avoid overestimation of the likely benefits (and feasibility) of such socially and economically costly interventions (19).

In conclusion, confidence in the effectiveness of antiviral neuraminidase inhibitor drugs to prevent and treat pH1H1 disease appeared to have been borne out in published reports plus data presented at the Options Conference. Nonetheless, the need for further studies to better define their effect when initiated very early in the course of illness remains as one of several still unanswered questions of contemporary clinical importance.

Antiviral drug resistance and new therapeutic modalities for influenza viruses

Neuraminidase inhibitors (NAIs) such as oseltamivir (Osel) and zanamivir (Zan) are the first-line agents for the treatment of influenza A and B virus infections. Prior to the 2009 A/H1N1 pandemic, there was a global spread of the H275Y Osel-resistant A/H1N1 virus (A/Brisbane/59/2007-like) that seemed to be independent of drug use. The good fitness of this Osel-resistant but Zan-susceptible H275Y mutant virus was probably due to the prior introduction of a series of NA mutations that increased its NA activity and

allowed the introduction of the H275Y mutation. Since 2009, the A/Brisbane/59/2007 (H1N1) strain has been replaced by the pandemic A/H1N1 virus (pH1N1) of swine origin. Early studies showed that the new pH1N1 strain was inherently resistant to the adamantane inhibitors (amantadine and rimantadine) but was highly susceptible to the NAIs.

Dr Charles Penn from WHO indicated that, as of August 2010, 304 Osel-resistant (Zan-susceptible) pH1N1 viruses have been reported to WHO representing approximately 1% of tested isolates. All but one virus harboured the H275Y NA mutation previously associated with Osel-resistance in seasonal A/H1N1 viruses and also in A/H5N1 viruses. The other Osel-resistant virus had the I223R NA mutation. Among these 304 cases, 86 (28%) were immunocompromised individuals, 98 (33%) were treated immunocompetent subjects, 19 (6%) were patients who had received post-exposure prophylaxis, 28 (9%) were patients without a history of antiviral use and finally 73 (24%) were preliminary notification cases. Although there have been 3 cases clusters where transmission of drug-resistant viruses might have occurred, there is no evidence of widespread community circulation of Osel-resistant pH1N1 viruses at this moment. In general, the immunocompromised patients constitute the most important setting where resistance may emerge and these patients should be treated more aggressively using increased and prolonged doses of Osel. If Osel resistance is suspected, inhaled Zan is the only available alternative for treatment. Dr Larisa Gubareva from CDC in Atlanta reported the U.S. drug susceptibility data for pH1N1 viruses. Out of > 4000 viruses tested, 100% were resistant to the adamantanes due to the S31N mutation in the M2 gene with one strain also containing the V27A M2 mutation. Out of > 8000 viruses tested, 71 (0.9%) were resistant to Osel due to the H275Y mutation in the NA gene. There were a few outlier viruses with decreased drug susceptibility that contain NA mutations at codons 223, 313 and 427. The detection of NAI resistance in influenza viruses is currently performed by genotypic methods (PCR followed by conventional sequencing or pyrosequencing) which can be done directly on clinical

samples and/or by phenotypic methods (NA inhibition assay) which can be done only on culture isolates. A poster update of the IRIS study (Schutten et al.), which is an observational multicenter surveillance study in Osel-treated and untreated patients, revealed that only 1/492 (0.2%) enrolled patients had a H275Y mutant. In that trial, Osel treatment resulted in faster virus clearance of pH1N1 virus compared with those not treated.

One of the important aspects of drug resistance discussed by several speakers and summarized by Dr Fred Hayden (University of Virginia) is the question of the transmission potential of the Osel-resistant pH1N1 virus. At least 4 studies performed in ferrets and, to a lesser extent, in guinea pigs have examined this question (Hamelin et al., PLoS Pathogens 2010; Duan et al. PLoS Pathogens 2010; Seibert et al., J Virology in press; Kiso et al., PLoS Pathogens 2010) and some of them were presented in great details at the meeting. In these animal models, it seems that the H275Y Osel-resistant virus is as virulent as its wild-type drug-susceptible counterpart when clinical, virological and histopathological endpoints were examined. The transmission of the mutant virus by direct contact seems preserved although some but not all groups have reported that airborne transmission of the mutant may be delayed or compromised compared to the wild-type virus. This discrepancy could be explained by the different pH1N1 strains studied and the experimental set-up that was used.

There were several oral and poster presentations on investigational antiviral and immunomodulatory approaches for the treatment of influenza infections as summarized by Dr Fred Hayden (University of Virginia). First, there are other NAIs in development such as IV peramivir (phase 3 in US but already approved in Japan), IV Zan (which should move to phase 3 soon) and laninamivir. The latter drug is a long-lasting NAI that is administered through a single inhalation. The results of a phase 3 clinical trial comparing two different single doses of laninamivir to multiple doses of Osel were presented by Dr Norio Sugaya from Japan. Other antiviral drugs with different viral targets that are currently evaluated in humans include favipiravir (T-705), a viral RNA polymerase inhibitor which is orally bioavailable, and also

DAS181, a recombinant sialidase protein that remove cell surface sialic acids. A combination of 3 antivirals (amantadine, Osel and ribavirin) has shown in vitro activity against amantadine-and Osel-resistant influenza A viruses (Nguyen, PLoS One 2010) and clinical trials should be initiated soon. Experimental antiviral agents in pre-clinical evaluation include Cyanovirin-N, a protein that binds on oligosaccharides at the surface of the hemagglutinin and nitazoxanide, a thizolide compound that blocks the maturation of the hemagglutinin. Other non-antiviral and immunomodulatory approaches that were discussed include the use of convalescent blood products (anecdotal reports in severe pH1N1 infections), human monoclonal antibodies that bind to the stalk of the hemagglutinin molecule (Japp Goudsmit, Netherlands), selective COX-2 inhibitors (Suki Lee, Hong Kong), small molecules that induces interferon (Mila Ortigoza, New York), statins (D Fedson), peroxisome proliferator-activated receptor (PPAR) agonists including fibrates and glitazones, small interfering RNA (si RNA) molecules designed to inhibit viral or host gene expression, etc. The efficacy of an antiviral (Zan) and immunomodulators (celecoxib and mesalazine) was shown to be beneficial in reducing A/H5N1 virus infection mortality in mice (Zheng et al. PNAS 2008) and other combination therapy approaches are being investigated in animal models.

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