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Meeting Report

Report of the first Asia–Pacific Forum on antiviral treatment of influenza, Asia–Pacific Alliance for the Control of Influenza, Bangkok, 14 June 2012

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On 14 June 2012, the Asia–Pacific Alliance for the Control of Influenza (APACI) convened the first Antiviral Forum jointly with the Influenza Foundation of Thailand and the Thailand Department of Disease Control. The goals of the meeting were to improve pandemic planning in the region from lessons learned during the 2009 pandemic, particularly with regard to the safety and efficacy of antiviral use; gain a better understanding of the therapeutic use of antivirals in seasonal influenza; review and analyse the official influenza control policies of Asia–Pacific countries and evidence gaps to support policy development; and to establish collaborative relationships to promote best practices in the use of antivirals for the treatment of influenza. The urgent need for education highlighting the importance of influenza and the benefits of antiviral drug use in the Asia–Pacific region was identified.

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Introduction

The Asia–Pacific Alliance for the Control of Influenza (APACI) held their first Antiviral Forum 14 June in Bangkok, Thailand, with the key objectives to:

- Improve pandemic planning in the region from lessons learned during the 2009 pandemic, particularly with regard to antiviral drug safety and efficacy.
- Gain a better understanding of the therapeutic use of antiviral drugs in seasonal influenza.
- Review and analyse the official influenza control policies of Asia–Pacific countries and identify evidence gaps to support policy development.
- Establish collaborative relationships to promote best practices in the use of antiviral drugs for the treatment of influenza.

Three presentations reviewed aspects of the antiviral treatment of influenza, followed by a challenging clinical discussion involving the audience on personal experiences and practices.

Historical aspects

Professor Frederick Hayden (The Wellcome Trust, UK, and University of Virginia, Charlottesville, USA) presented an overview of the history of influenza antiviral drug development from the 1960s and highlighted our understanding of the mechanism of action of both the M2 ion channel inhibitors (amantadine and rimantadine) and the neuraminidase inhibitors (such as oseltamivir and zanamivir), as well as the development of antiviral resistance.[1–3] The frequency of M2 inhibitor resistance due to the S31N mutation in the A (H3N2) and the current A(H1N1)pdm09 viruses remains high, with all strains tested being resistant. As a result, the M2 inhibitors are no longer recommended for the primary treatment or prophylaxis of influenza A infections. Resistance to oseltamivir became a major issue in 2008 following the emergence and global transmission of the A(H1N1) seasonal viruses carrying the H275Y mutation.[4] Other mutations in this virus allowed it to retain full fitness, so that it caused illness comparable to oseltamivir-susceptible virus and had greater ability than susceptible strains to spread, ultimately replacing the susceptible virus.[5] That virus has now been replaced by A(H1N1)pdm09, which has shown low levels (~1–2%) of resistance. While most cases with mutations were immunocompromised patients who had received prolonged antiviral treatment, resistant virus has been detected in treatment naive persons, including an increasing fraction of isolates from the community.[6] In several instances, resistant viruses have caused nosocomial or

community clusters in absence of selective drug pressure. Thus, we must remain vigilant and have ongoing surveillance for influenza viruses with resistance mutations in place.

More effective therapy of severe influenza and in the treatment of high-risk patients, especially the immunocompromised, is needed. Intravenous neuraminidase inhibitors, peramivir and zanamivir, are available for severe influenza, but only on an investigational basis.

A number of new drugs are in development and into phase 1 and 2 trials, including neutralising human monoclonal antibodies that have heterosubtypic antihaemagglutinin specificity.[7]

Optimisation of differing dosing regimens and combinations is required. Different combinations of two neuraminidase inhibitors showed effects that varied from synergistic to antagonistic, including one clinical trial which found that zanamivir and oseltamivir together were less effective than oseltamivir alone in treating uncomplicated influenza.[8,9] The inclusion in treatment regimens of antivirals to which the viruses are resistant is problematic; however, triple combination therapy for amantadine- or oseltamivir-resistant viruses in cell culture has shown promise. Adding ribavirin to amantadine and oseltamivir produces a highly synergistic combination that is significantly better than double combinations, and this regimen is undergoing clinical testing.[9]

Summary:

- There is substantial progress in the development of intravenous neuraminidase inhibitors, other novel antiviral agents, therapeutic antibodies and antiviral combinations.

Lessons from the 2009 pandemic

Professor Alison McGeer (Dalla Lana School of Public Health, University of Toronto and Director of Infection Control, Mount Sinai Hospital, Toronto Canada) provided an overview of antiviral therapy in pregnancy and in neonates. Prior to 2009, there was a lack of data about antiviral therapy from controlled clinical trials in pregnant women, so that during the 2009 pandemic, clinicians had to try a range of treatment strategies. Antiviral treatment during pregnancy improved maternal and foetal outcomes including reduced severity of disease with early treatment and reduced need for ICU care (31% versus 57%) for treatment commenced within 48 hours of onset with a lower but significant benefit from later treatment.[10,11] Some safety and pharmacokinetic data on oseltamivir have been obtained, but uncertainty remains regarding transplacental transfer.[12–14] Current CDC recommendations endorse early treatment based on clinical suspicion, rather than delaying decisions until test results are available.[15]

Antiviral use in children during the pandemic clearly indicated that early treatment reduced the severity of disease in terms of ICU admission and death.[16] The odds ratio for death after early treatment was 0.2(0.07–0.54) in comparison with late treatment.[17] The CDC strongly recommends early treatment of children <2 years of age who are at high risk of influenza complications.[15]

As regards influenza transmission in households, prophylaxis of household contacts was effective; however, treatment of the index case within 48 hours was more effective than prophylaxis of contacts and more effective than hand washing.[18,19] There are now excellent data on outbreak management using antiviral drugs.[19,20] The use of 'ring prophylaxis' in Singapore to contain an outbreak in a military establishment is a clear demonstration of effectiveness in a large closed setting.[21] More caution may be needed in outbreaks amongst teenagers as they may be at increased risk of adverse events that include self-injury or delirium.[22]

Challenges include the early recognition of an influenza outbreak by public health practitioners and the ability to intervene rapidly. In addition, antiviral resistance may also arise, so testing and ensuring adequate infection control practices in high-risk settings are important. Accurate and understandable communication with patients can be difficult. While messages regarding pregnant women are usually straightforward, in a study of COPD patients over 25% of respondents found information available confusing. An additional challenge exists, as even at the peak of influenza activity, only 50% of patients meeting a case definition have influenza, so it is difficult to know which will benefit from treatment. Laboratory-based testing is too slow to assist with early treatment decisions, and the current point of care tests are unsatisfactory as they have sensitivities of only 20–65%, so we clearly need better and more available diagnostics.

Summary:

- Early antiviral treatment (within 48 hours of onset) of hospitalised patients with antiviral drugs is important in reducing the risk of severe illness and death, although treatment commenced later than this may still benefit patients with severe disease.
- Neuraminidase inhibitors can be used effectively for the control of influenza in household and other closed settings, although greater caution is needed in outbreaks amongst adolescents due to an increased risk of adverse events.
- Early identification of outbreaks and early intervention pose challenges for public health practitioners.
- Clear communication with risk groups is important.
- Better rapid diagnostic tests are needed to assist early antiviral treatment decisions.

Practical aspects of antiviral treatment of influenza in adults

Professor Nelson Lee (Department of Infectious Diseases, Department of Medicine and Therapeutics, The Chinese

University of Hong Kong) spoke about the treatment of influenza in Hong Kong, which had provided a unique setting for the evaluation of the use of antiviral agents in severe infection due to seasonal and pandemic influenza. In seasonal influenza, large observational studies suggest better clinical and virological outcomes in hospitalised patients treated with neuraminidase inhibitors (NAIs): shortened viral shedding, reduction in length of hospital stay and reduced mortality.[23] These benefits are greatest amongst the immunocompromised and, in those patients, are present even when treatment is initiated 48–96 hours after onset.[20]

Similarly with pandemic H1N1, numerous studies in hospitalised patients suggest timely NAI treatment is associated with enhanced viral clearance, shortened length of stay and improved survival of pregnant and immunocompromised patients and that with some patients, efficacy persists even when initiated 48–96 hours after symptom onset.[23] Better outcomes and improved cost-effectiveness were seen with empirical NAI treatment, in comparison with using delaying treatment until a PCR-based diagnosis was made.[24,25]

Issues with the delivery of NAIs to severely ill patients were discussed. Inhalation of NAIs has advantages and disadvantages: delivery is challenging in those with impaired inspiratory effort as it may induce bronchospasm, it has limited penetration to lung periphery and it has no systemic distribution. In severe pneumonia, systemic availability of NAIs is required, and the intravenous NAI peramivir is approved in Korea and Japan and for emergency use in the United States. Intravenous zanamivir and oseltamivir are both available through compassionate-use programmes. The long-acting inhaled NAI laninamivir appears to have a similar efficacy to 5 days of oseltamivir treatment.[26]

Timing of treatment is important. Initiation of treatment at the earliest possible time is consistently associated with better outcomes for outpatients and hospitalised patients with seasonal influenza and hospitalised patients with pandemic H1N1 influenza. The risk of ICU admission and death from pandemic H1N1 increases 20% per day of delay in commencing treatment.[27,28]

Optimal dosing for treatment for H5N1 and pandemic H1N1 pneumonia in patients remains uncertain.[29] Higher than standard doses of oseltamivir are generally well tolerated but there is little evidence of difference in virological and clinical responses. The conventional duration of treatment is for 5 days for mild seasonal influenza, with extended treatment for pneumonia. Prolonged viral shedding, especially in immunocompromised patients and in patients following delayed treatment, increases the risk of virological and clinical relapses following treatment.[30] Therefore, the total duration of treatment depends on both symptom resolution and the determination of viral clearance in lower respiratory tract samples by PCR. Antiviral susceptibility also varies across influenza types and subtypes with a lower clinical response for influenza B than for influenza A and a higher risk of resistance emerging for H1N1 compared with H3N2 viruses. The close monitoring of antiviral resistance, especially in immunocompromised patients, is essential.[31]

Summary:

- Observational studies suggest better clinical and virological outcomes in hospitalised patients treated with neuraminidase inhibitors.
- Early antiviral treatment based on a clinical diagnosis achieves the best outcomes, but later therapy still provides benefits.
- The mechanisms by which increased availability of intravenous antiviral agents can affect outcomes for severely ill patients with influenza pneumonia should be studied.
- More data are needed on the dosing and duration of therapy in severely ill patients, including immunocompromised patients.

Discussion on personal experiences and practices

Associate Professor Tawee Chotpitayasunondh (Queen Sirikit National Institute of Child Health, Department of Medical Services, Ministry of Public Health, Thailand) focused on the lessons learned from human infections during the avian influenza outbreak from 2003 to 2012 in South-East Asia and reinforced the need for clinical judgement in treatment decisions to ensure antiviral use as early as possible after the onset of symptoms. The underlying condition of the patient, the disease severity and the time since symptom onset are all important factors to consider in patients with suspected or confirmed influenza requiring hospitalisation.[15,29] He challenged the audience over 'Why influenza was prioritised as a low public health problem in most limited-resource countries?' In many countries, public health authorities believe influenza to be a mild, self-limiting disease of little importance essentially because of the lack of disease burden data. Despite the lessons learned in the region since 2003, limited surveillance of seasonal influenza and linked diagnostic capacity for human infections, along with the competing priorities for limited resources, has restricted the use of antiviral agents for the treatment of seasonal influenza.

Summary:

- There is a lack of influenza disease burden data in the Asia–Pacific region.
- The associated lack of recognition of the importance of influenza has led to underutilisation of antiviral drugs for the treatment of influenza.

Conclusions

- Early antiviral treatment of influenza is pivotal, and initiation should not be hindered because of the lack of an influenza test result, especially during peak seasonal activity when the accuracy of a clinical diagnosis is reasonably high.
- There is an urgent need for education highlighting the importance of influenza, its burden and the benefits of antiviral drug use in the Asia–Pacific region.

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