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Part I: STATIN THERAPY: WHERE ARE WE TO DATE? Only available on the website.
Part II: OSELTAMIVIR IN THE MANAGEMENT OF INFLUENZA IN ADULT PATIENTS

Introduction

Influenza is a common and underrated seasonal illness and every year adults and children worldwide are affected. Typically annual outbreaks of influenza epidemics occur in winter months. A substantial demand is inflicted on the healthcare resources and industry each year resulting from increased primary care consultation, drug treatment, clinical complications, referrals, hospitalisations and work absenteeism.[1]

Influenza is debilitating, and a typical case can restrict activity for 5 to 6 days, can cause 3 to 4 days of bed disability and 3 days lost from school or work.[2]

Although rare, global outbreaks called *pandemics* can occur, with significant epidemiological impact. Three pandemics were recorded during the 20th century: the Spanish influenza pandemic in 1918, the so-called 'Asian virus' in 1957 and the most recent pandemic that originated in Hong Kong in 1968-1969. These pandemics caused widespread deaths.[1,3]

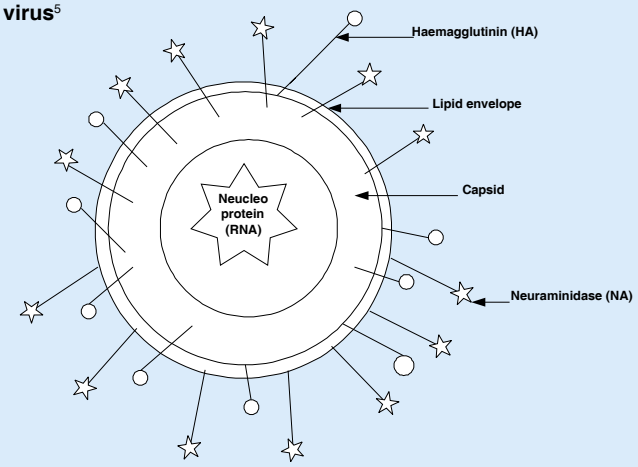
Recently a new influenza A strain (H5N1) has been detected in birds from Southeast Asia. The virus has spread to humans and has already caused more than 60 deaths. Based on the fact that 2 of 3 criteria for a pandemic have been met, the WHO (World Health Organization) has warned that an avian influenza (H5N1) pandemic is looming.[1]

The influenza virus

Viral Structure

The influenza virus is a helically shaped, RNA virus of the orthomyxovirus family.[1,4] The capsid mainly consists of two antigenic proteins, haemagglutinin (HA) and neuraminidase (NA), protruding through the lipid layer.[1] (Refer to Figure 1) There are 16 HA subtypes (H1-6) and 9 different NA subtypes (N1-9).[1]

Figure 1: Schematic illustration of the structure of the *Influenza* virus[5]



Influenza Antigen Types

The influenza virus is categorised into 3 basic antigen types, A, B and C, based on differences in their nuclear material.[1,4] Influenza A and B each have 8 segments of RNA and influenza C has 7 segments.[1] Influenza A is categorised into further subtypes based on differences in surface antigens HA and NA.[4] In humans H1, H2 and H3 are involved in the attachment of virus to cells; N1 and N2 are involved in the process of viral penetration into cells.[4] Clinical features vary between the different subtypes. General characteristics of the influenza viruses are:[4]

Influenza A

- Affects all ages
- Infects animals and humans
- Causes moderate to severe illness
- Natural reservoir of virus is aquatic birds
- Most influenza A viruses are not pathogenic to their natural hosts and do not mutate

Influenza B

- Mainly affects children
- Only in humans
- Causes milder disease

Influenza C

- Not prone to cause epidemics
- Rarely reported in humans as most cases are subclinical

Kaji *et al* did a study to determine the difference in clinical features between certain strains. Patients were divided into 3 groups to compare symptoms and laboratory data for Influenza A H1N1, A H3N2 and Influenza B infections. The study results showed that in Influenza A H3N2-infected patients the fever, leukopenia and increase in C-reactive protein were more severe than in subjects with Influenza A H1N1 or Influenza B infections. Fever, general malaise and sore throat were equally frequent in influenza A H3N2, A H1N1, and B infections. Gastrointestinal symptoms were more common in influenza B.[6]

Viral Life Cycle

The influenza virus is spread from person to person via droplets from coughs or sneezes or other contaminated surfaces or material. The influenza virus then attaches to the host's cell-surface receptors in the upper and lower airway. The virus then enters the cells and the viral RNA uncoating occurs within minutes. The viral genes are then replicated inside the cell nucleus within approximately 6 hours.[1]

Distinctive features of RNA virus replication include high mutation rates, high yields and short replication time.[7] Antigenic drift refers to the virus's ability to overcome the

body's immune system by means of mutation within the viral antibody-binding sites. This is caused by a minor change in surface antigen and may occur in all 3 influenza types. This may result in an epidemic.[4] On the other hand, antigenic *shift* occurs if there is a *major* change at the NA or HA surface antigens, resulting in the emergence of a new strain of Influenza A. This is a sudden change in antigenicity that happens when a cell is simultaneously infected by two different strains of type A influenza, and could potentially cause a pandemic.[4,5]

The enzyme *neuraminidase*, projecting from the surface of the influenza virus, allows the recently-formed viral particles to leave infected cells and spread throughout the body.[8,9]

Drug Prophylaxis and Treatment

One of the biggest challenges in the prophylaxis and treatment of influenza is the genetic variability of the RNA viruses which enable them to overcome vaccine or drug protection.[1] As vaccines inhibit or reduce the likelihood of interspecies transfer, an influenza vaccine remains the ideal way to reduce the spread of the influenza viruses. However vaccination is not always a management option as the preparation of a new vaccine takes 6 months or more.[3]

There are two classes of antiviral drugs available for prophylaxis and treatment of influenza virus:[3,4]

- M2 ion channel blockers (amantadine and rimantadine)
- NA inhibitors (zanamivir and oseltamivir)

In South Africa only amantadine (Symadin®; Symmetrel®) and oseltamivir (Tamiflu®) are available. Symmetrel® is also registered for the treatment of Parkinson's syndrome.

Amantadine

Amantadine blocks the ion channel activity of the M2 protein of most influenza A viruses. By blocking the hydrogen ion flow the viral replication is inhibited when the virus enters the host.[3] Amantadine however has no activity against influenza B viruses. In addition drug resistant variants develop rapidly in treated patients.[2,3]

Oseltamivir

Oseltamivir is a prodrug, the metabolite of which is a potent and specific influenza neuraminidase (NA) inhibitor that inhibits replication of a wide variety of influenza A and B viruses,[1,2,9,10] including the avian influenza virus H5N1.[1] This NA inhibitor blocks an established infection in the late stages by blocking the release of virions from infected cells. This decreases the spread to other cells by inhibiting the viral penetration of mucous secretions.[3]

Indications and Dosing Schedule

Oseltamivir (Tamiflu®) was registered by the MCC (Medicines Control Council) in February 2006 for the following indications:

- The treatment of influenza in adults and children ≥ 1 year of age
- Prophylaxis of influenza in adults and adolescents ≥ 13 years of age[9]

Tamiflu® is currently available at a single exit price (SEP) of R199.50 for 10 capsules. Although Tamiflu® can be taken with or without food, enhanced tolerability in some patients may occur when taken with food.[9]

It is recommended that **treatment** should commence within the first or second day of the onset of influenza symptoms. In adults and children >40kg or ≥8 years, 75mg twice daily for 5 days is required. [9]
Prophylaxis should be commenced within 2 days following contact with an infected person. The dose required is 75mg once daily for at least 7 days. The duration of protection lasts for as long as dosing is continued. [9]

Efficacy of oseltamivir in treating acute influenza

In a double-blind, stratified, randomised, placebo-controlled, multi-centre trial of 374 patients conducted during the influenza epidemic season from January to March 1998 in the United States, oseltamivir treatment reduced the severity of acute influenza in otherwise healthy adults. A decrease in the incidence of secondary complications was also suggested.[2]

The inclusion criteria for this study were:

- Adult patients between the ages of 18-65 who presented within 36 hours from onset of influenza symptoms
- Oral temperature had to be 38°C or higher
- One or more respiratory symptom e.g. cough, sore throat or nasal symptoms
- One or more constitutional symptom e.g. headache, malaise, myalgia, sweats and/or chills or fatigue

These patients were then randomly assigned to one of three treatment groups:

- Oseltamivir, 75mg orally twice daily for 5 days
- Oseltamivir, 150mg orally twice daily for 5 days
- Placebo twice daily for 5 days

The participants recorded symptoms, their oral temperature and their ability to perform usual activities. In addition, participants were asked to complete a visual analogue scale of their overall health status. Anterior nose and posterior pharyngeal throat swabs for isolation of influenza virus were taken at pre-defined intervals.

The primary efficacy end points were time to resolution of illness and severity of illness. Duration of illness, defined as the time from start of taking the study drug to the time that the symptoms were relieved, decreased by more than 30% ($p<0.001$) in both oseltamivir groups. In the placebo group this was 4.3 days, in the 75mg-group 3 days and in the 150mg-group 2.9 days. Overall, median severity of illness reduced by approximately 40% ($p<0.001$).The patients who received oseltamivir reported relief from the

illness within 24 hours after initiation of therapy more frequently in comparison with those patients who received placebo.[2]

In a meta-analysis by Kaiser et al, oseltamivir treatment in adults and adolescents with a proven influenza illness reduced overall antibiotic use for any reason by 26.7% and the incidence of influenza-related lower respiratory tract complications resulting in antibiotic therapy by 55%, relatively to placebo.[10]

Efficacy of oseltamivir for prevention of influenza A and B

A meta-analysis by Cooper et al showed a 74% (16%-92%) relative risk reduction in laboratory-confirmed influenza in 2 studies on seasonal prophylaxis of a healthy population group. Post-exposure prophylaxis in households showed a 90% (71%-92%) relative risk reduction in laboratory-confirmed influenza, and seasonal prophylaxis in an elderly population in residential care demonstrated a 92% (39%-99%) relative reduction in laboratory confirmed symptomatic flu.[11]

Resistance to NA Inhibitors

Given the fact that RNA viruses have high mutation rates,[7] the question of drug resistance to antiviral chemotherapy remains relevant.[1] Treatment with amantadine can cause resistant viruses in at least 30% of individuals.[11] Resistance to neuraminidase inhibitors has been observed infrequently in human studies. Resistance rates of <1% of treated adults and 4-8% of children have been reported.[1,3,12] However, rigorous detection techniques did identify resistant mutants in 9 out of 50 (18%) Japanese children during treatment with oseltamivir.[12]

Resistance of the influenza virus to NA inhibitors is associated with mutations of the viral NA. However, in animal models these mutations have been shown to decrease the stability of the NA, thereby compromising viral fitness, including compromised growth and transmissibility.[1,2,12] However, in a recent animal study Yen et al indicated that there is a substantial difference in the viral fitness and transmissibility depending on the different levels of NA functional loss during mutations.[12]

Conclusion

The only options available to control influenza infections are vaccines and antiviral chemotherapy.[12] The influenza vaccine remains the mainstay for prophylaxis of influenza A and B viruses, however the time required to develop a new vaccine makes antiviral drugs a very important treatment option.[3]

Oseltamivir has been shown to be effective for the treatment of influenza A and influenza B infections. Intervention should however occur in the early stages of disease progression (i.e. 48 hours into viral replication) as this enhances the efficacy of the drug.[10] Although resistance is less frequent in patients treated with NA inhibitors[11], resistance to antiviral treatment regimens remains a concern. The unanswered question is whether the NA inhibitors will continue to provide sufficient levels of therapeutic and prophylactic effectiveness against the influenza virus and whether resistant versions will emerge.

In light of the cost of Tamiflu® and previous supply issues, another major concern raised on the role of antiviral drugs in the management of a looming avian 'flu pandemic was the availability and accessibility of these drugs to the target population.[3] In response to these concerns it was announced in May 2006 that Roche has entered into an agreement with Aspen Pharmacare to produce a generic version of oseltamivir for governments and not-for-profit organisations in the African sub-continent.

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