Influenza antiviral drugs: present and future

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ABSTRACT: Influenza causes annual epidemics and pandemics with increased morbidity and mortality. Antiviral agents with different chemical structure and mode of administration reduce the duration of symptoms, the risk of complications and death. The emergence of viruses with resistance against adamantanes and neuraminidase inhibitors drives research on additional influenza antivirals.

Keywords: Influenza, antiviral drugs, neuraminidase inhibitors, clinical trials

INTRODUCTION

BInfluenza is an infectious disease caused by an influenza virus. There are 3 types of seasonal influenza viruses: A, B and C. Type A influenza viruses are further classified into subtypes. Among many of them, influenza A(H1N1) and A(H3N2) subtypes, as well as type B, are currently circulating among humans. Type C influenza cases occur much less frequently than A and B. There is also a new influenza virus type identified as D. Type D primarily affects cattle and is not known to infect or cause illness in people.

Seasonal influenza is an acute viral respiratory infection that has a very efficient human transmission mode. It is characterized by a sudden onset of symptoms: high fever, cough, headache, muscle and joint pain, severe malaise and sore throat, usually described as Influenza-Like-Illness (ILI). Common complications include pneumonia, ARDS and increased risk of death in high-risk groups. Worldwide it is estimated to result in about 3 to 5 million cases of severe illness and about 250000-500000 deaths annually.[1]

Various antiviral agents against influenza viruses are available in different countries. Antiviral drugs, when timely administered, relieve symptoms and shorten the duration of illness by 1 or 2 days. They can also reduce the risk of complications and death.[2] Ideally, antiviral drugs need to be administered within 48 hours from the onset of symptoms. However later administration, even after 3-5 days from the onset of symptoms, has been proven to still reduce the risk of complications and death, especially among high risk individuals.[2] Antiviral drugs are usually prescribed for 5 days, although hospitalized influenza patients may require treatment for a longer period.

There are 2 classes of antiviral drugs for influenza: The adamantanes, amantadine and rimantadine-which are matrix protein inhibitors and the neuraminidase (NA) inhibitors. NA inhibitors are oseltamivir, zanamivir, peramivir and laninamivir.

Adamantanes

The antiviral drugs amantadine and rimantadine, inactivate the viral ion channel (M2 protein), thus inhibiting replication of the influenza A virus. The mechanism of function is by utilizing the fact that influenza viruses need acidic pH for the uncoating process. M2 protein is responsible for forming a membrane pore allowing the hydrogen ions that generate the acidic environment to enter into the viral particle. Adamantanes cause blockage of the M2 channel, thus inhibiting the virus from becoming acidic. Inhibition of the M2 protein function will therefore inhibit viral uncoating and reduce viral replication and disease progression.[3]

The first adamantane was used as an antiviral drug

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in 1967. The adamantanes are well absorbed orally and the usual adult dose for influenza A is 100 mg orally, twice a day. After four decades of effective use of the adamantane class of antiviral drugs in the prophylaxis and treatment of influenza, global resistance against these drugs has increased dramatically among influenza viruses of the A(H3N2) and A(H1N1) subtypes in recent years. In the vast majority of cases, the basis for resistance is conferred by an S31N amino acid variation at the M2 protein of currently circulating A(H1N1)pdm09 and A(H3N2) viruses. Resistance to the adamantane class of antiviral drugs by human A(H3N2) influenza viruses currently exceeds 99% in Europe, USA, many Asian countries and also in Greece. [4,5]

In addition, amantadine has been associated with several central nervous system (CNS) side effects, likely due to amantadine's dopaminergic activity. Amantadine can be prescribed to relieve the symptoms of the Parkinson disease. CNS side effects include nervousness, anxiety, agitation, insomnia and difficulty in concentrating. Rimantadine can produce gastrointestinal effects such as nausea and upset stomach. Most importantly, the increased viral resistance limits the use of the adamantanes for the treatment of influenza, although these drugs still have a place in planning for prophylaxis during future epidemics.[6]

Neuraminidase inhibitors

The neuraminidase inhibitor (NAI) class of influenza antivirals first circulated in 1999 and now includes four compounds: oseltamivir (TAMIFLU®), zanamivir (RELENZA®), peramivir (RAPIVAD®) and laninamivir (INAVIR®).[7] These differ in chemical structure, bioavailability and mode of administration.

The neuraminidase inhibitor class of influenza antivirals selectively inhibit the neuraminidase (NA) of both influenza A and B viruses. These two types of viruses possess neuraminidase on their outer surface, an enzyme essential for the release of newly formed viral particles from infected cells, for the prevention of viral aggregates formation and for the viral spread within the respiratory tract. The neuraminidase inhibitors are structural analogs of sialic acid, which is the substrate of neuraminidase (NA) and the receptor for the influenza virus. The neuraminidase inhibitors bind to the substrate binding site of NA, thus blocking its enzymatic activity. This results to viral aggregation on the host cell surface and reduction in the amount of virus that is released and spread to infect other cells.[8]

The recommended dosage of zanamivir for treatment of influenza in persons aged ≥12 years is two inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart) for 5 days and the recommended dosage of oseltamivir for treatment in patients aged ≥18 years is 75 mg is by oral administration, twice daily for 5 days. Peramivir is approved and recommended for use in adult patients of over 18 years of age. The dosage is 600 mg via intravenous infusion for 15 -30 minutes.[2]

Emergence of viruses with reduced NAI susceptibility has been observed over the last decade both on a local and global scale. For example in late 2007 former seasonal A(H1N1) viruses acquired the neuraminidase H275Y amino acid substitution which conferred oseltamivir resistance, impacted clinical effectiveness and spread globally in less than 12 months.[9] More recently, clusters of A(H1N1)pdm09 viruses containing the H275Y substitution, have been detected in Hokaido, Japan and Pennsylvania, USA, probably due to the extensive use of the drugs.[10] Molecular analysis of the neuraminidase gene of 34 influenza A(H1N1)pdm09 virus strains that circulated during 2010-2011 in Northern Greece showed that two of them also possessed the known resistance mutation H275Y, whereas the rest were susceptible to oseltamivir. Two resistant A(H1N1)pdm09 viruses were also identified during the first introduction of the virus in the pandemic period.[11,12] According to a previous study and to the WHO report, the resistance mutation is more frequently induced by the use of oseltamivir to the patient, rather than spontaneously occurring and persisting to the viral population.[11,13]

Careful use of antiviral drugs will limit the threat of emerging antiviral resistance against NAIs. In the majority of countries, only oseltamivir and inhaled zanamivir are approved, with oseltamivir being the most widely used. The policy of using influenza antivirals differs around the world. Countries such as Japan and the USA use the greatest volumes of drugs and regularly treat influenza virus infected patients presenting at general practitioners or hospital outpatient clinics, while other countries, such as Greece, primarily use the drugs to treat severely ill patients.[14] Overall, based on current analysis, >99% of influenza viruses tested during 2014-2015 were susceptible to all four NAIs, indicating that these antivirals remain

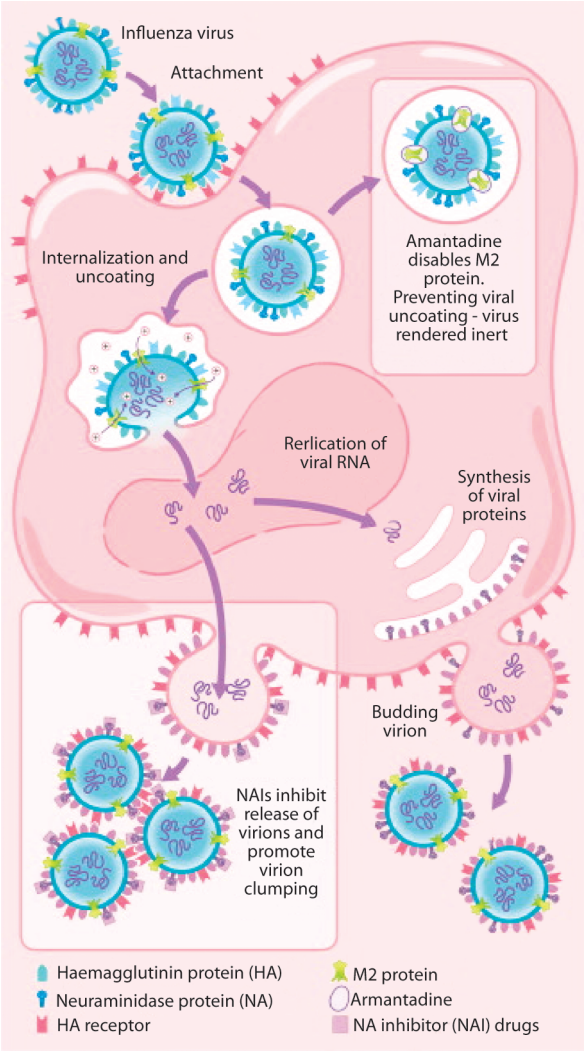

Figure 1: The mechanism by which antiviral drugs interrupt the replicative cycle of influenza is illustrated. Amantadine blocks viral internalization and uncoating. Neuraminidase inhibitors prevent the neuraminadase from releasing budding viruses and dispersing virions.

Photo:Myra Rudakevich

an appropriate choice for the treatment and prophylaxis of influenza virus infections. Specifically, oseltamivir is considered to be the most appropriate drug for the treatment of severe cases.[14] Notably, NAIs have also limited side effects, most commonly nausea, vomiting and diarrhoea.

Novel anti-influenza agents

Emergence of antiviral drug resistance drives the research and development of other influenza antivirals that target viral proteins or host factors. Nitazoxanide, favipiravir and fludase are currently in late-phase clinical trials but they have not yet been approved for use in patients with uncomplicated influenza infections. Originally developed and commercialized as an antiprotozoal agent, nitazoxanide was later identified as a first-in-class broad spectrum antiviral drug and has been repurposed for the treatment of influenza. The drug blocks maturation of the viral hemagglutinin at the post-translational stage .The drug had no effect on the other glycoprotein, neuraminidase, the target of oseltamivir and zanamivir, or the M2 protein, the target of amantadine. A phase 2b/3 clinical trial was recently published reporting that oral administration of nitazoxanide, 600mg twice daily for 5 days, decreased the duration of clinical symptoms and reduced viral shedding compared to placebo in patients with laboratory-confirmed influenza.[15]

Favipiravir is an antiviral drug that selectively inhibits the RNA-dependent RNA polymerase of influenza virus. It has been found to inhibit all serotypes and strains of influenza A, B and C viruses against which it has been tested. It also inhibits influenza strains resistant to current antiviral drugs, and shows a synergistic effect in combination with oseltamivir. Favipiravir directly inhibits viral replication and transcription. A Phase III clinical evaluation of favipiravir for influenza therapy has been completed in Japan and two Phase II studies have been completed in the United States.[16]

The development of fludase has been pioneered by NextBio, a US start up biopharmaceutical company that specializes in developing antiviral agents. In the human respiratory tract, cell surface sialic acids act as host cell receptors for influenza A and B viruses. Fludase works by removing sialic receptors from the airway epithelium, therefore preventing viral entry into cells of the respiratory epithelium. Fludase completed the initial preclinical development and entered clinical development to determine its efficiency and safety in humans. In preclinical studies, fludase displayed potent antiviral activity against clinical influenza isolates of the highly pathogenic H5N1 subtype of avian influenza A.[17]

INDICATIONS

Generally, individuals at higher risk for influenza complications recommended for antiviral treatment include: children aged under 2 years, adults aged 65 years and older, pregnant or postpartum women, individuals with chronic pulmonary, cardiovascular, re-

nal, hepatic, haematological or metabolic disorders and immunosuppressed people. Notably, two of the antiviral drugs, oseltamivir and zanamivir, are approved for children. Oseltamivir (Tamiflu®) is recommended by the CDC and American Academy of Pediatrics for the treatment of influenza for children aged 2 weeks and older, and for the prevention of influenza in children aged 3 months and older. Zanamivir (Relenza®) is recommended for the treatment of influenza in children aged 7 years and older, and for the prevention of influenza in children aged 5 years and older.[2]

Influenza antiviral drugs can also be administered for chemoprophylaxis. Antiviral medications are approximately 70% to 90% effective in preventing influenza and are useful adjuncts to influenza vaccination.[2] Widespread or routine use of antiviral medications for chemoprophylaxis is not recommended, in order to limit the possibility of emerging antiviral resistant viruses. However, chemoprophylaxis is suggested for influenza prevention in individuals that belong to the aforementioned high-risk groups after exposure to an infectious patient during the first two weeks following vaccination and in individuals with severe immune deficiencies or others that might not respond to influenza vaccination.

Clinical judgement on use of antiviral drugs and/or antibiotics on a patient with typical ILI symptoms is very important. Rapid Influenza Diagnostic Tests (RIDTs) can help determine the treatment decision. They can be useful to identify influenza virus infection as a cause of respiratory local outbreak and epidemic. Positive RIDT results from one or more patients with suspected ILI can support decisions to promptly implement infection prevention and control measures for influenza outbreaks. These RIDTs are immunoassays that can identify the presence of influenza A and B viral nucleoprotein antigens in respiratory specimens, and rapidly display the result in a qualitative way. RIDTs could assist in the reduction of unnecessary antibiotic prescriptions, in cases when antiviral drugs would be more beneficial for the patient. Most importantly, despite their use both for the prevention and treatment of influenza, antiviral drugs cannot serve as a substitute for the influenza vaccine. Effective vaccination is considered the best way to prevent seasonal influenza, while antiviral drugs will always stand at the first line of defence for the treatment of the actual disease.

List of abbreviations:

CNS- Central Nervous System
ILI- Influenza-like-illness
M2- Matrix Protein 2
NA- Neuraminidase
NAI- Neuraminidase inhibitors
RIDTs - Rapid Influenza Diagnostic Tests

Αντιικά φάρμακα για την γρίπη: παρόν και μέλλον

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Περίληψη: Η γρίπη προκαλεί ετήσιες επιδημίες και πανδημίες με αυξημένη νοσηρότητα και θνησιμότητα. Αντιικοί παράγοντες με διαφορετική χημική σύσταση και θεραπευτική προσέγγιση μειώνουν τη διάρκεια των συμπτωμάτων, τις επιπλοκές και το θάνατο. Η ανάδυση ιών με ανθεκτικότητα στις αδαμαντάνες και στους αναστολείς της νευραμινιδάσης οδηγεί σε ανάγκη για ανακάλυψη νέων αντιικών φαρμάκων.

Λέξεις κλειδιά: γρίπη, αντιικά φάρμακα, αναστολείς νευραμινιδάσης, κλινικές δοκιμές

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