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Prospects for Specific Influenza Treatment

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ABSTRACT

Influenza is an acute respiratory disease caused by the flu virus. The influenza virus is a RNA-containing virus that causes mass epidemics and pandemics. There are currently many ways in which influenza can be specifically prevented and treated. Specific influenza prevention includes vaccination. However, the antigenic variability of the virus reduces the effectiveness of the vaccine. Specific therapy for influenza infection includes several classes of drugs, among them neuraminidase (NA) inhibitors - oseltamivir, zanamivir, and M2-protein inhibitors - amantadine, rimantadine. The widespread use of these drugs and the high variability of the influenza virus lead to a gradual loss of their pharmacological effect. Among the new developments of antiviral drugs, we should mention histidyl-1-adamantyl ethylamine, which is a modification of the molecule of Rimantadine and at the stage of preclinical studies showed sufficient antiviral activity. A representative of another class of drugs - arbidol, hemagglutinin (HA) inhibitor of the influenza virus. According to research data, this drug has high efficacy and safety profiles, but the World Health Organization's recommendation is to continue clinical trials. Clinical trials of new classes of drugs - baloxavir marboxyl and favipiravir - are currently underway. Baloxavir marboxyl is an inhibitor of the cap-dependent endonuclease. Favipiravir is an inhibitor of RNA-dependent RNA polymerase. Preclinical studies have shown high efficacy of these drugs. The rapid evolution of the influenza virus leads to a gradual decrease in the effectiveness of modern antiviral drugs. In this regard, the improvement and development of antiviral drugs is an urgent task.

Keywords: antiviral activity, baloxavir marboxyl, favipiravir, influenza virus, neuraminidase inhibitors, rimantadine derivatives.

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INTRODUCTION

Influenza is one of the most common respiratory diseases. In most cases, the disease is not a concern, and the infection goes away on its own. However, severe influenza can lead to serious complications, including death. Annually, according to the World Health Organization (WHO) data for 2005, between 3 and 5 million serious cases of the disease and approximately 250,000 to 500,000 deaths are registered worldwide, and as of 2018, the mortality rate was between 290,000 and 650,000 per year[1]. At the same time, the highest mortality rates are mainly observed for persons over 65 years of age and children under 2 years of age. The cause of this disease is an RNA-containing influenza virus. The high variability of viral RNA and mutations caused by progressive antigenic drift cause annual influenza epidemics and an increase in the number of lethal outcomes[2]. Specific and non-specific therapies are currently used to treat and prevent influenza infection[3]. Specific therapy includes two classes of drugs, such as neuraminidase inhibitors and M2-protein inhibitors. Specific prophylaxis is carried out using influenza vaccines. Interferon and interferon inducers are used for non-specific influenza treatment. Higher rates of mutation in the genetic material of the influenza virus and the development of resistance to current drugs are driving the global scientific community to develop new or improve existing drugs for the treatment and prevention of influenza infection.

This review contains detailed information on the antiviral drugs currently in use in medicine, as well as substances that may become drugs for the treatment and prevention of influenza virus in the future.

GENERAL CHARACTERISTICS OF THE INFLUENZA VIRUS

Influenza virus belongs to the Orthomyxoviridae family and includes 4 genera: A, B, C and D. Influenza D virus has been recently detected in cattle in the USA[4], B and C infect only humans, and influenza A virus is zooanthroponosis. Influenza A has the highest species diversity, with about 18 serotypes, which differ in variations in the influenza virus's main surface antigens, hemagglutinin~~in~~ (HA) and neuraminidase (NA), making influenza A the main etiologic factor for annual influenza epidemics and pandemics[5]. These proteins play an important role in the life cycle of the influenza virus. Thanks to HA, the virus adheres to the host cell and then penetrates the cell. Neuraminidase is a transmembrane glycoprotein that separates virions from the host cell, contributing to the subsequent development of the infection[6]. HA and NA are the main proteins of the influenza virus, which are targeted by antiviral immunity, so in the process of evolution, mainly these proteins are subjected to mutating. At present, 18 HA subtypes and 10 NA subtypes are described in the influenza A virus[7]. The M2 protein also plays an important role in the penetration of the virus into the cell. It represents a tetramer proton-selective channel, which, by pumping hydrogen ions into the virion, contributes to the uncoating of the virus and the release of RNA[8]. These proteins are the targets of drugs widely used in medicine. Prolonged use of the same drugs leads to the emergence of influenza virus resistance to these drugs. To overcome this problem in the development of new pharmaceutical substances, the search for new targets is carried out, as well as chemical modification of existing molecules.

SPECIFIC PREVENTION OF INFLUENZA

Currently, there are no drugs that protect against influenza virus by 100%. The most effective method of specific prevention is vaccination. There are three main types of influenza vaccines[9]. Live attenuated vaccines contain attenuated virions and are administered intranasally. Although this type of vaccination is the closest to a natural infection, the effectiveness is not always justified, since when injected through the nose, the amount of virus entering the body is not constant. In addition, live vaccines, as the most reactogenic ones, often cause allergic reactions and complications, therefore, they are not recommended for use in children under 2 years old and elderly patients. Inactivated vaccines contain killed whole or split virions, and are administered subcutaneously, while the dosage of the virus completely enters the body, but the vaccination procedure is unpleasant, pain, redness, and swelling appear at the injection site. Subunit vaccines are composed of viral proteins, namely HA and NA, exhibiting pronounced antigenic properties. These vaccines are the safest, as they are free from foreign proteins that can cause serious side effects. However, the reactogenicity of such vaccines is the smallest, because not whole virions are introduced, but only their components.

The most frequent seasonal epidemics are caused by influenza A H1N1 and H3N1 and, to a lesser extent, influenza B viruses. Based on these, annual influenza vaccines are developed. However, the rapid variability of influenza A caused by antigenic HA and NA drift, leads to a decrease in the effectiveness of vaccination due to the lack of cross-immunity to different strains of the virus[10]. This means that every 2-3 years, or even annually, new vaccines should be developed based on the strains of the virus circulating at that time. Studies in the United States have shown that the effectiveness of vaccination in 2017-2018 was 36%, 67% against influenza A (H1N1), 42% against influenza B and 25% against influenza A (H3N2)[11]. Research on the development of innovative influenza vaccines is currently intense. In 2017, a vaccine based on hemagglutinin of influenza A H7N9 was developed in the United States and is currently undergoing clinical trials[12]. A live attenuated vaccine against the H3N2 influenza strain, which was developed in the United States in 2018, has proven to be effective and safe in adults and is currently being tested in children[13].

NEURAMINIDASE INHIBITORS

Neuraminidase is a surface protein of the influenza virus that plays an important role in the spread of the virus between target cells. It exhibits enzymatic activity by breaking down the α-glycosidic bond between sialic (N-acetylneuraminic) acid on the cell surface and the sugar residue of the HA virus[14]. In this case, the resulting virions are able to split off from the cell membrane and infect neighbouring cells. Also, the enzymatic activity of NA promotes the passage of the virus through the mucous membrane of the respiratory tract, rich in sialic acids[15].

In the 1990s, drugs inhibiting NA function were synthesized. They are analogues of sialic acid and compete with the active centre of NA, disrupting the release of viral offspring from an infected cell. Currently, NA inhibitors are the only drugs recommended for the treatment of influenza virus infections. The main NA inhibitors used worldwide are oseltamivir and zanamivir (Figure 1). Laninamivir is approved for use in Japan, while peramivir is approved for use in China, Japan, South Korea, and the United States[16].

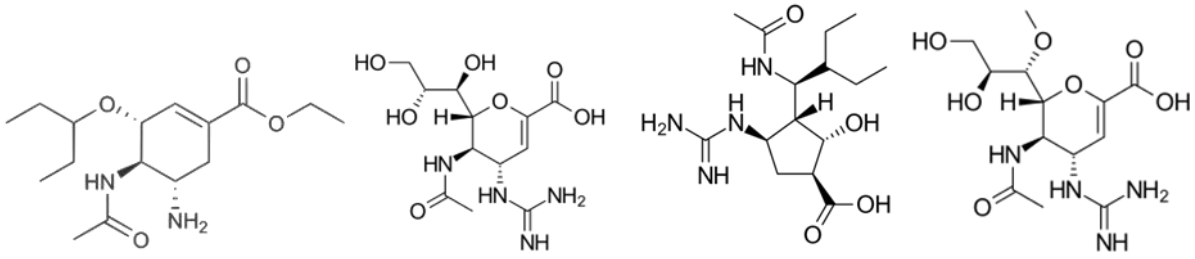


Figure 1. Structural formulas of neuraminidase inhibitors.

According to a randomized, placebo-controlled, double-blind study of the effectiveness of oseltamivir, when this drug was administered orally at a dosage of 75 mg, there was a 21% reduction in the time of manifestation of flu symptoms (from 122.7 hours to 97.5 hours) compared with the placebo group condition of taking the drug immediately after the onset of the first symptoms[17]. At the same time, the efficiency of other drugs was generally comparable to that of oseltamivir. Due to the low bioavailability, zanamivir and laninamivir are administered by inhalation, while peramivir is administered intramuscularly, which causes some limitations in use, unlike orally administered oseltamivir.

Between 2007 and 2009, influenza viruses resistant to NA inhibitors were detected, with resistance increasing in some cases from 1% to 90% over this period[18,19]. Influenza viruses resistant to NA inhibitors were found to have several mutations in the neuraminidase gene, of which H274Y was the most common. This resulted in conformational changes in NA and impaired drug binding to it. At present, most influenza viruses are still susceptible to NA inhibitors, but the evolution of the influenza virus may change everything in the opposite direction. In this regard, it is necessary to develop new drugs that will not only overcome resistance but will also be able to increase the effectiveness of the treatment of influenza infections at a later stage of the disease.

Chinese scientists have synthesized new compounds that inhibit the activity of influenza virus neuraminidase[20]. The compounds were modifications of the known drug oseltamivir. The new functional groups were associated with the guanidine fragment of oseltamivir (Figure 2).

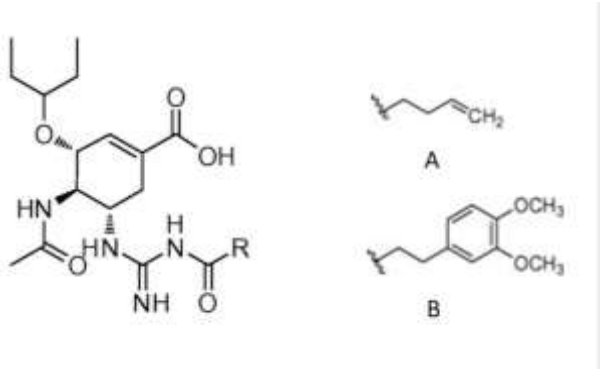


Figure 2. Oseltamivir derivatives that have the most pronounced activity against the influenza virus. R = A or B.

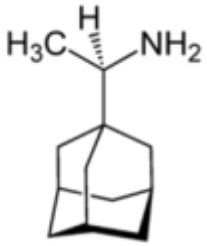
The antiviral activity of these compounds in vitro exceeded the activity of oseltamivir by 5 times (derivative A) and by 11 times (derivative B). In addition, influenza strains H1N1 and H3N2, resistant to oseltamivir, were sensitive to the above derivatives. Thus, these compounds are recommended for further studies as influenza virus neuraminidase inhibitors.

M2 CHANNEL INHIBITORS

Some highly pathogenic human viruses, such as influenza A virus, human immunodeficiency virus 1, hepatitis C virus produce proteins capable of forming ion-conducting pores in the membrane - viroporins[21]. They disrupt the ionic homeostasis of the target cell in favour of the virus to ensure proper replication and assembly of viral particles. Influenza A virus M2 protein oligomerizes and integrates into the viral envelope, forming a proton-selective ion channel. The M2 channel plays an important role in the penetration of influenza virus into the cell and creates the necessary conditions for the assembly of viral particles[22]. The acidification of the contents of the endosome formed after the virus enters the cell activates the M2 channel, and protons are pumped into the virus. The acidic medium promotes the dissociation of RNA and the protein complex, as well as the cleavage of the viral membrane and the subsequent release of RNA into the cytoplasm of the cell for subsequent replication.

Since 1966, the only antiviral drugs that inhibit the function of the M2 channel of the influenza virus and are approved for medical use are adamantane derivatives - amantadine and rimantadine (Figure 3).

Amantadine



Rimantadine

Figure 3. Structural formulas of M2 channel inhibitors.

Adamantane derivatives have been used for many decades to prevent and treat influenza. According to studies, amantadine reduced the incidence of influenza A by an average of 61%, and the duration of flu symptoms decreased by about 1 day[23]. At the same time, rimantadine had comparable efficacy with amantadine, but due to the lack of a sufficient number of trials, prevention data was not statistically significant. However, the intensive use of M2 channel inhibitors led to the emergence of resistance of influenza viruses to them. According to US epidemiological surveillance worldwide, from 1995 to 2004. there was an increase in the resistance of influenza viruses to amantadine and rimantadine from 0.4% to 12.3%, respectively[24]. In the US, this growth ranged from 1.9% to 14.5%. Genotyping of influenza A viruses isolated in 2005 showed that more than 90% of all isolates with resistance to adamantanes contained point mutations in the M2 protein gene. This led to amino acid substitutions in the protein itself. The most common substitution was S31N (replacing serine in position 31 with asparagine)[25]. According to the US Centers for Disease Control and Prevention, at present, almost 100% of influenza viruses are resistant to amantadine and rimantadine[26], so the further use of these drugs for the prevention and treatment of influenza infection is inappropriate. The introduction of additional functional groups into the molecules of adamantanes is likely to be able to revive the antiviral activity of these drugs during subsequent development.

Preclinical trials of a new promising drug, a derivative of rimantadine - histidyl-1-adamantylethylamine (H-His-Rim) are currently underway (Figure 4).

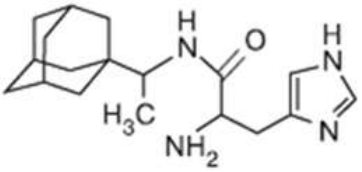


Figure 4. The structural formula of histidyl-1-adamantylethylamine (H-His-Rim).

In vitro studies of this drug in MDCK cell culture showed that H-His-Rim reduced the reproduction of influenza A (H1N1)pdm virus by 91%, A (H3N2) by 94%[27]. In vivo tests were performed on mice. In this case, the effectiveness of the drug was lower than in cell culture and amounted to about 40%[28], and the toxicity of the compound was lower than that of rimantadine.

It is known that the cause of resistance of influenza viruses to amantadine and rimantadine are amino acid substitutions in the M2-channel. S31N substitutions have been found to predominate in adamantadine resistant influenza viruses[25]. The second most common mutation is V27A (replacement of valine in position 27 with alanine)[29]. In the USA, a compound (Figure 5), a derivative of adamantane was synthesized that showed inhibitory activity against influenza viruses with the V27A mutation[30].

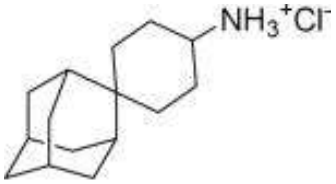


Figure 5. The structural formula of spiroadamantane amine.

In an in vitro test on a cell model, spiroadamantane amine showed a high degree of inhibition of influenza virus (95.2%) at an EC_{50} of 0.3 ± 0.1 μM. In in vivo studies in mice, this compound at a dose of 100 μg/kg provided 90% animal survival, prevented weight loss and pulmonary hemorrhage.

Thus, H-His-Rim and spiroadamantane amine can be considered as promising substances for clinical trials.

HEMAGGLUTININ INHIBITORS

Hemagglutinin (HA) is a homotrimeric glycoprotein that fuses and penetrates the influenza virus into the target cell, is of no small importance when infected with the influenza virus[31]. Receptors to HA are sialic acid residues on the surface of sensitive cells. When they interact with hemagglutinin, a receptor occurs - mediated endocytosis and the virus in the form of endosomes penetrate into the cell. A decrease in pH in the endosome leads to conformational changes in HA and the viral and cell membranes merge, after which the virus genetic material is transported to the cell nucleus for replication. HA is the most promising target for antiviral drugs, as such drugs inhibit the initial stage of infection by preventing the virus from entering the cell.

Currently, the drug arbidol (umifenovir) is presented on the pharmaceutical market as an HA inhibitor (Figure 6).

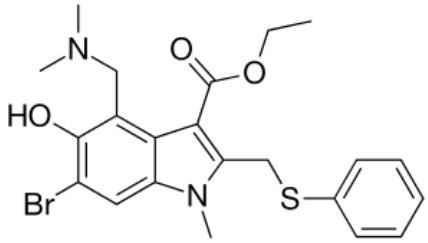


Figure 6. The structural formula of arbidol (umifenovir).

Arbidol has been used in Russia as a means of influenza treatment and prevention for over 20 years. Studies of the mechanism of action have shown that arbidol binds to hemagglutinin of the influenza virus and stabilizes it, preventing the binding of HA to receptors of the target cell[32,33]. According to the data of clinical trials of arbidol the efficacy and safety as well as preventive effect of arbidol were higher than those of NA and M2-protein inhibitors[34]. The use of arbidol for influenza infection reduced the average duration of the disease by approximately 2 days. In this case, compared with rimantadine, there were no complications in patients with chronic diseases. In studies of arbidol as a prophylactic against the influenza virus, it was found that the number of cases decreased by 86% compared with the control group. Another advantage of arbidol over the previously listed drugs is the high sensitivity of influenza viruses to it. Analysis of isolates isolated between 2004 and 2005 did not reveal a single strain resistant to arbidol[35].

Thus, according to many years of research, arbidol is highly effective against the influenza virus, has a pronounced prophylactic effect, and is also well-tolerated. However, according to the WHO report[36], data on the effectiveness of arbidol are doubtful, information on clinical trials is insufficient to meet the requirements of evidence-based medicine, therefore, WHO recommends that the results of studies be interpreted with caution.

Intensive research and development of drugs that have an inhibitory effect on influenza hemagglutinin are currently underway. Of particular interest are drugs based on monoclonal antibodies. In 2009 - 2011, there were studies of the preparations CR6261[37] and CR8020[38] based on human monoclonal antibodies to HA influenza virus. It was shown that these drugs had a neutralizing effect against 5 strains of the influenza virus H5N1 and H1N1. When used in mice within 5 days after infection, they were protected from death. These drugs are currently undergoing phase 2 clinical trials to evaluate the effectiveness of influenza-infected patients.

INFLUENZA DRUGS OF OTHER CLASSES

In 2018, it became known about conducting clinical trials in Japan[39] of a new unique antiviral drug in its class - baloxavir marboxil (Figure 7).

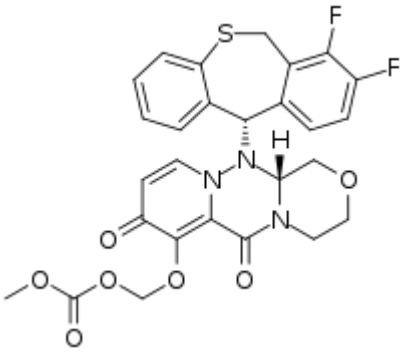


Figure 7. The structural formula of baloxavir marboxyl (xoflusa).

Baloxavir action is connected with suppression of influenza virus replication[40]. After the virus enters the cell and releases genomic RNA, mRNA is initially synthesized for further viral particle production. The mRNA synthesis

is initiated by cap-dependent endonuclease, which forms a primer for viral RNA polymerase. Baloxavir binding to the cap-dependent endonuclease blocks its function and the subsequent synthesis of mRNA.

According to clinical trials, baloxavir had sufficient efficacy against the influenza virus, the use of the drug led to a reduction in the duration of symptoms by about a day (23-28 hours), compared with the placebo group. An obvious advantage of baloxavir is its single-use within the first 48 hours after the appearance of symptoms. Currently, the drug is approved only in Japan and the United States, and with the successful use of baloxavir is likely to be on the world market.

Favipiravir is another experimental antiviral drug that is also being studied in Japan (Figure 8).

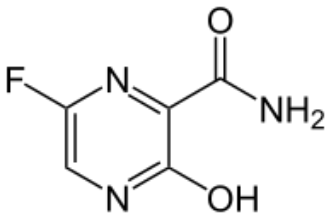


Figure 8. Structural formula of favipiravir.

According to the results of studies, favipiravir revealed activity against a wide range of RNA-containing viruses, such as influenza virus (A, B and C), West Nile fever virus, yellow fever virus, foot and mouth disease virus [41], and also in a mouse model shown efficacy against Ebola virus. Favipiravir, like baloxavir, blocks the replication of the influenza virus, directly affecting its reproduction. Its target is the RNA-dependent RNA polymerase, an important enzyme for replication. At the stage of preclinical studies, favipiravir showed higher in vitro and in vivo efficacy and safety compared to NA and M2 protein inhibitors[42]. The drug is currently undergoing phase 3 clinical trials in Japan and the United States. With a wide range of antiviral activity, favipiravir has a high chance of breaking the lead among anti-influenza drugs.

CONCLUSION

Influenza is one of the main public health problems. The most effective way to fight influenza is through prevention. The basis of prevention is the annual vaccination. However, vaccines need to be periodically updated due to new variations of the influenza virus. Modern flu therapy includes two main classes of compounds - NA inhibitors and M2 protein inhibitors. M2 blockers, such as amantadine and rimantadine, have lost their relevance due to the development of high resistance to influenza viruses. Neuraminidase inhibitors oseltamivir, zanamivir are still effective against influenza infection, but the emergence of influenza viruses resistant to them leads to restrictions in the use of these drugs. To overcome resistance to NA and M2-protein inhibitors, intensive development of new derivatives such as histidyl-1-adamantayl ethylamine, spiroadamantane amine is underway. They have successfully completed preclinical trials and are currently candidates for clinical trials. The Russian drug arbidol (umifenovir) has shown high efficacy and safety in clinical trials, but according to WHO experts, its effectiveness needs to be further investigated. Baloxavir and favipiravir are a new generation of antiviral drugs that are at the stage of studying the efficacy and safety of patients with influenza. Upon completion of clinical trials, drugs can be included in the list of the most effective means for the prevention and treatment of influenza infection.

CONTRIBUTION OF THE AUTHORS

All authors participated in the collection of information, its analysis, discussion and writing the text of the article.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

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