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Antiviral Resistance in Influenza Virus: Mechanism of Action

Weichen Lyu

The Ohio State University, Columbus, Ohio, The United States, 43210

l18611553100@gmail.com

Abstract. The "Spanish flu" pandemic caused by H1N1 virus in 1918 caused 50 million deaths. The best-known drugs for treating influenza viruses are antiviral drugs, including amantadine, rimantadine, zanamivir, and oseltamivir. Amantadine and rimantadine are excellent prophylactic drugs against influenza A. Whereas, Zanamivir and oseltamivir have comparable efficacy against influenza A and B viruses. This paper reviews antiviral drugs, approved for clinical use. This review evaluates neuraminidase inhibitors (NAIs), focusing on their mechanism of action and the emergence of resistance to them. The results showed that the viruses mutated and developed resistance during the treatment with NAIs for seasonal, pandemic, and avian influenza.

Keywords: influenza, mutation, antiviral drug, RNA inhibitors, prevalence

1. Introduction

Seasonal influenza viruses (A/H3N2, A/H1N1, B), pandemic influenza viruses (H1N1pdm09), and avian influenza viruses (A/H5N1, A/H7N9) are the main types of influenza viruses that rapidly mutate to produce new viruses with symptoms such as coughing, sore throat, vomiting, and sore muscles. Influenza viruses are now one of the most prevalent viruses that cause respiratory infections, infecting about 5-15% of the population [1]. Viruses that cause influenza can significantly increase the number of hospitalization, and they are a lot more harmful to the human body than we might assume. Four major inhibitors are used in treating the influenza virus with pharmaceuticals. These include neuraminidase inhibitors (NAIs) (oral: zanamivir, injectable: oseltamivir), M2 inhibitors (amantadine, rimantadine), viral RNA inhibitors (ribavirin), and polymerase inhibitors (favipiravir)[2]. In this article, we will concentrate on NAI inhibitors and the drug resistance that they exhibit, analyze the performance and mechanisms of these drugs for seasonal influenza, pandemic influenza, and avian influenza viruses, summarize the benefits and drawbacks of these drugs, and talk about the mechanisms of these drugs as well as their clinical implications. This study serves as a foundation for future research into the principles and treatment of the influenza virus.

2. Analysis

This chapter will mainly focus on three different kinds of viruses: Seasonal Influenza viruses (A/H3N2, A/H1N1, B), Pandemic influenza viruses. (A/H1N1pdm09) and Avian influenza viruses (A/H5N1, A/H7N9).

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2.1. Seasonal influenza viruses (A/H3N2, A/H1N1, B)

The two most common influenza A and seasonal viruses, H3N2 and H1N1, have extraordinarily high rates of severe disease, with a peak prevalence from May to October. The H3N2 influenza virus is the leading cause of human influenza illness and mortality globally because of how easily it can spread [3]. These two viruses in humans typically cause a runny nose, sore throat, vomiting, and exhaustion, which are symptoms similar to the common flu. However, fever, body aches, and persistent coughing are signs of influenza viruses. The invasion of the H3N2 virus into the human body, which occurs when the virus gets past many levels of defense and enters the pharynx, illustrates the seasonal influenza virus's invasion process [3]. To successfully attach to the surface of the cell membrane, it locates a cell with a sialic acid receptor on the cell membrane. It uses hemagglutinin to bind to the receptor. The virus is accepted into the cell because it believes it is a protein. The virus enters the cell to release its matrix and envelope proteins, releasing RNA polypeptidase and ribonucleoprotein RNP (a mix of ss-RNA and ribonucleoprotein NP) (for transcription). Ribonucleoprotein RNP degrades into ss-RNA and nucleoprotein NP at the start of replication. RNA polymerase uses ss-RNA as a template to create ss+RNA. A portion of ss+RNA is directly employed as a template to generate the viral gene ss-RNA.

In contrast, the remaining portion is partially encoded by RNA polymerase to produce matrix protein, hemagglutinin H, neuraminidase N, nucleoprotein NP, RNA polymerase, and RNA splicing non-structural protein. Finally, the mature nucleocapsid is assembled within the cell membrane with hemagglutinin H and neuraminidase N to obtain the envelope. The new virus is released from the bud onto the cell membrane surface. Matrix proteins assemble the nucleoprotein NP, ribonucleoprotein RNP, and RNA multimers to form a completely new viral nucleocapsid at cytoplasmic maturity [4]. To release the new virus into bodily fluids and infect other cells, neuraminidase hydrolyzes sialic acid. Flu is treated and prevented by antiviral drugs called neuraminidase inhibitors (NAIs). By restricting the action of the enzyme neuraminidase, NAIs avoid the release of new viral particles. Oseltamivir-resistant seasonal influenza viruses have been detected more frequently lately (2% in adults and 5%–18% in children). 14% of influenza A/H1N1 strains in Europe were oseltamivir-resistant in 2007, according to published data [5].

The symptoms of the seasonal virus include fatigue, chills, fever, body aches, headache, sore throat, runny or congested nose and cough. The changes in the structure of the virus, such as the binding to NA proteins of a flu virus can significantly reduce the ability of the antiviral drug Oseltamivir. This result in seasonal drug-resistant virus strains [6]. Since people with influence have a high rate of hospitalization, it is essential to avoid infection. The best practices to avoid infections are the administration of vaccination, adhering to cough etiquette and respiratory hygiene, appropriate management of infected patients, implementing environmental safety measures and adhering to health information [7]. The best practice to increase the effectiveness of the treatment is to consult the doctor as soon as the symptoms are present and strictly adhere to the treatment plan recommended by the doctor.

2.2. Pandemic influenza viruses (A/H1N1pdm09)

The first pandemic of the twenty-first century began in April 2009 when a new virus first surfaced in Mexico and California (US). It is unconnected to any currently circulating inter-pandemic viruses and spreads quickly from person to person. The new virus was designated as A/(H1N1) pdm09. It is a quadruple reassorting virus made up of two viruses with swine origins, one with avian origins and one with human sources. More specifically, molecular analyses have discovered the European and Asian "avian-like" swine H1N1 viruses, the North American H3N2 triple reassorting viruses, and a traditional swine H1N1 virus [8]. Since then, H1N1 has developed epidemiological traits similar to seasonal influenza, and H1N1 (pdm09) has steadily taken over as the pathogen of H1N1 flu. In the influenza seasons of 2012–2013 and 2014–2015, H1N1 dominated seasonal influenza globally [9].

The 2014 H1N1 influenza pandemic in India resulted in thousands of fatalities. About 450,000 people in mainland China contracted influenza in 2017, with a 33.1/per 100,000 incidence rate [10]. The predominant influenza strain in mainland China during the 2017–2018 influenza season was H1N1. Mainland China's sentinel hospitals reported more excellent outpatient and emergency influenza-like

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illnesses in 2017 than in the previous three years and a higher positive rate for influenza virus testing. Additionally, many more influenza outbreaks were reported than during the year before. Hospitalizations for influenza with confirmed cases as well as severe cases increased. The antigenic evolution of the seasonal influenza virus facilities an increase in infectious capacity. Here is his strain of the influenza virus containing haemagglutinin [11]. However, there was no difference in viral transmissibility, disease severity, or viral treatment resistance for the common influenza viruses. Due to its simple oral administration, oseltamivir is the preferred medication for therapy. However, zanamivir (intravenous or inhalation) is frequently used when oseltamivir's effectiveness is diminished, such as when resistance develops. Over five months, a Danish team examined the usage of zanamivir and oseltamivir in a patient with the virus. It looked into whether viral resistance had emerged and discovered that the H1N1pdm09 virus only needed one mutation (H275Y) to cause resistance to oseltamivir [12]. This suggests that influenza viruses are more resistant to zanamivir than oseltamivir. Figure 1 shows the timeline of immunocompromised influenza patients with zanamivir and oseltamivir obtained in the study. Less resistance was observed to zanamivir than to oseltamivir. This might be because oseltamivir is used more frequently than zanamivir.

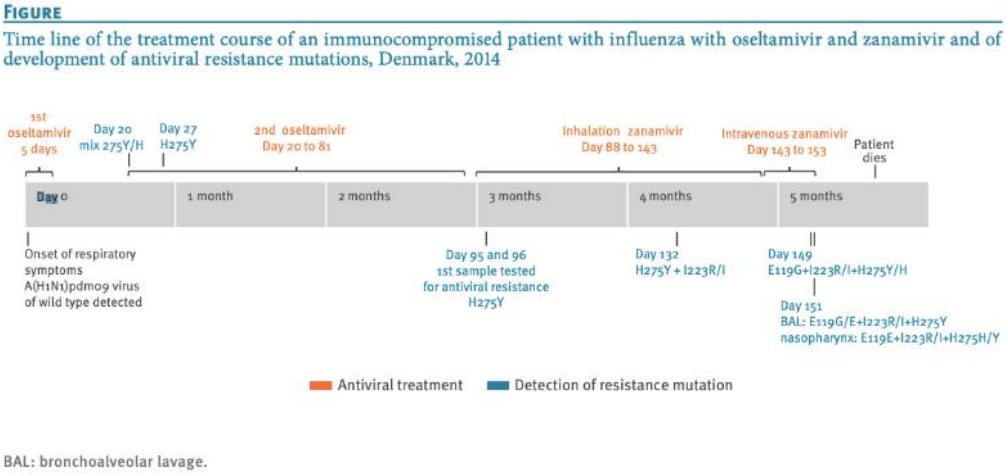


Figure 1. The timeline of immunocompromised influenza patients with zanamivir and oseltamivir [12].

2.3. Avian influenza viruses (A/H5N1, A/H7N9)

The influenza A virus is known as the avian influenza virus (AIV). The three varieties of influenza viruses—A, B, and C—belong to the orthomyxovirus family of RNA viruses. They include influenza A viruses, which are primarily found in birds but can also infect humans and other mammals like pigs, horses, seals, and whales. Influenza B and C viruses are more commonly associated with the infection of seals and pigs, respectively.

Polymorphic, with a vesicular membrane and a spherical form measuring 80–120 nm in diameter. Single- and negative-stranded RNA fragments make up the genome.

According to the antigenicity of the hemagglutinin (H) and neuraminidase (N) proteins found on the outer membrane, there are 16 H subtypes (H1 to H16) and 9 N subtypes (N1 to N9) [13]. The three primary avian influenza virus subtypes that infect humans are H5N1, H9N2, and H7N7, the latter of which causes severely unwell individuals with a high fatality rate. It is viral influenza in birds; a contagious illness brought on by the influenza A virus that can manifest in birds as anything from mild respiratory symptoms to severe systemic septicemia. The OIE classified avian influenza, which is easily spread among birds and is referred to as "chicken plague" in folklore, as an infectious disease of category A. Ion channel inhibitors, which target the ion channel protein M2 of influenza viruses and prevent the replication of influenza viruses by interfering with the ion channel activity of the M2 protein, are the first major class of chemical drugs used to treat influenza. Outbreaks of avian influenza occurred in

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Australia, Italy, Hong Kong, China, the Netherlands, and the Netherlands in 1994, 1997, 1999, and 2003, respectively, and in 2005 [13]. These outbreaks were primarily in Southeast Asia and Europe. Ion channel inhibitors are the first, and they work by blocking the ion channel activity of the influenza virus's M2 ion channel protein to prevent the virus from replicating. The second is a neuraminidase inhibitor, which is an inhibitor that specifically targets the neuraminidase NA of the influenza virus. By blocking the activity of this enzyme, it effectively prevents the release of virus particles onto the surface of host cell membranes, preventing the infection of new host cells with the influenza virus. Patients with H5N1 avian influenza have also developed drug-resistant strains of this medication. There are also some synthetic analogs of sialic acid oligosaccharides, as well as single and compounded herbal remedies, but for a variety of reasons, none of them is easily spread on a large scale [17]. NAI therapy has been associated with positive clinical outcomes, and in vitro research demonstrates that it is susceptible to oseltamivir, peramivir, and zanamivir but resistant to adamantanes (S31N mutation, M2 numbering). In severe cases, secondary resistance (e.g., R294K, N9 numbering) is anticipated to emerge throughout treatment and may cause a rebound in viral load and clinical progression. Oseltamivir and peramivir are extremely resistant to the R294K mutant, although zanamivir and zanamivir are moderately less vulnerable to it. Notably, it may be difficult to identify phenotypic resistance because there may be a mix of resistant and wild-type viruses. To reduce the transmission of the influence A virus it is essential to get the vaccination, adhere to health information, implement environmental safety measures and appropriately management of the infected patients [6].

3. Conclusion

This essay focused on the performance and mechanisms of these drugs for seasonal influenza and pandemic influenza. Antiviral resistance in three influenza strains was discussed. In the case of seasonal influenza, it was noted that the Oseltamivir-resistant seasonal influenza viruses had been detected. In Pandemic influenza, less resistance was observed to zanamivir than to oseltamivir. Among the avian strains of influenza, Oseltamivir and peramivir are resistant to the R294K mutant, while zanamivir and laninamivir are moderately less vulnerable to it. Antiviral resistance in seasonal influenza, pandemic influenza, and avian influenza is a severe problem for modern medicine, as the constant use of the same drugs for different viruses significantly increases antiviral resistance, leading to the worldwide spread of those viruses that are highly infectious and have a considerable impact on human health. The lack of updated information on the status of drug-resistant influenza was a shortcoming of the article. Future research should concentrate on new drugs which can inhibit these drug-resistant strains and new treatment options to prevent the widespread infection due to these viral mutations. Research into new drugs will be even more painful, especially since resistance to NAIs has a significant effect because this drug is widely used worldwide.

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