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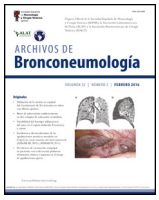

Review

Anti-Influenza Treatment: Drugs Currently Used and Under Development☆

Luciano Amarelle,[a,b] Emilia Lecuona,[a] Jacob I. Sznajder[a,*]

[a] Division of Pulmonary and Critical Care, Feinberg School of Medicine, Northwestern University, Chicago, IL, United States
[b] Departamento de Fisiopatología, Hospital de Clínicas, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay

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ABSTRACT

Influenza is a very common contagious disease that carries significant morbidity and mortality. Treatment with antiviral drugs is available, which if administered early, can reduce the risk of severe complications. However, many virus types develop resistance to those drugs, leading to a notable loss of efficacy. There has been great interest in the development of new drugs to combat this disease. A wide range of drugs has shown anti-influenza activity, but they are not yet available for use in the clinic. Many of these target viral components, which others are aimed at elements in the host cell which participate in the viral cycle. Modulating host components is a strategy which minimizes the development of resistance, since host components are not subject to the genetic variability of the virus. The main disadvantage is the risk of treatment-related side effects. The aim of this review is to describe the main pharmacological agents currently available and new drugs in the pipeline with potential benefit in the treatment of influenza.

Tratamiento Antigripal: Fármacos Actualmente Utilizados y Nuevos Agentes en Desarrollo

Palabras clave:
Gripe
Virus influenza
Tratamiento
Fármacos

RESUMEN

La gripe es una enfermedad contagiosa altamente prevalente y con significativa morbimortalidad. El tratamiento disponible con fármacos antivirales, de ser administrado de forma precoz, puede reducir el riesgo de complicaciones severas; sin embargo, muchos tipos de virus desarrollan resistencia a estos fármacos, reduciendo notablemente su efectividad. Ha habido un gran interés en el desarrollo de nuevas opciones terapéuticas para combatir la enfermedad. Una gran variedad de fármacos han demostrado tener actividad antiinfluenza, pero aún no están disponibles para su uso en la clínica. Muchos de ellos tienen como objetivo componentes del virus, mientras que otros son dirigidos a elementos de la célula huésped que participan en el ciclo viral. Modular los componentes del huésped es una estrategia que minimiza el desarrollo de cepas resistentes, dado que estos no están sujetos a la variabilidad genética que tiene el virus. Por otro lado, la principal desventaja es que existe un mayor riesgo de efectos secundarios asociados al tratamiento. El objetivo de la presente revisión es describir los principales agentes farmacológicos disponibles en la actualidad, así como los nuevos fármacos en estudio con potencial beneficio en el tratamiento de la gripe.

Introduction

Influenza is an infectious disease caused by various types of influenza virus, characterized by a highly contagious, acute respiratory syndrome. It usually presents in a mild form which resolves after 3–7 days, but it can also lead to other secondary infections or present in more severe forms, such as pneumonia or acute respiratory distress syndrome, which can be fatal, particularly in elderly

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* Corresponding author.
E-mail address: j-sznajder@northwestern.edu (J.I. Sznajder).

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Table 1
Anti-Influenza Drugs.

Drugs currently in use	
M2 ion channel inhibitors	*Neuraminidase inhibitors*
Amantadine	Oseltamivir
Rimantadine	Zanamivir
	Peramivir
	Laninamivir
Other pharmacological groups	
Drugs that act against viral components	*Drugs that act against host components*
Viral binding and fusion inhibitors	Binding inhibitors
MBX2329	DAS181 (Fludase®)
Arbidol	Aprotinin
Antibodies: CH65, D1-8, HB36.6	
	Endocytosis and fusion inhibitors
Viral polymerase inhibitors	Glycyrrhizin
Favipiravir (T-705)	LJ001
VX-787	Bafilomycin A1
	Concanamycin A
Nucleoprotein inhibitors	Saliphenylhalamide
Nucleozin	
Naproxen	Viral RNA transcription and transport inhibitors
	Geldanamycin
NS1 protein inhibitors	17-AAG
NSC125044	Ribavirin
JJ3297	Viramidine
Baicalin	
	Viral ribonucleoprotein complex export and post-transcriptional processes inhibitors
	Verdinexor
	Nitazoxanide
	Intracellular defense pathway inhibitors
	U0126
	PD-0325901
	AZD-6244
	AZD-8330
	RDEA-119
	Acetylsalicylic acid
	Other agents with anti-influenza activity
	Ouabain

patients.[1–4] Seasonal influenza affects 5%–10% of the world's population every year, producing around 3–5 million severe cases and between 250 000 and 500 000 deaths. Pandemic outbreaks with high mortality rates can occur, impacting severely on public health.[5]

Vaccination is essential in preventing both the disease and complications, which primarily occur in risk groups such as children, elderly patients, patients with chronic respiratory disease and pregnant women. If treatment with antivirals is administered without delay, the risk of severe complications can be reduced; however, many virus strains develop pharmacological resistance and lose efficacy, so there has been great interest in recent years in developing new therapeutic options for combating the disease. This review article describes the main pharmacological agents currently available, and analyzes new medications under study that show potential benefit in the treatment of influenza[5–7] (Table 1).

Structure and General Characteristics of the Influenza Virus

Influenza viruses belong to the *Orthomyxoviridae* family, and are classified as A, B or C. Influenza A viruses circulate in several species, including humans, horses and related animals, swine, and birds, while type B affects only humans. Influenza caused by types A and B is indistinguishable; in contrast, type C causes mild respiratory symptoms.[8–10]

The structure of influenza A virus consists of a lipid envelope that is generated from the host cell, to which hemagglutinin (HA) and neuraminidase (NA) glycoproteins are anchored. These surface antigens are used to classify the viruses (*e.g.*, H1N1, N3N2, H5N1). The outer membrane also contains matrix proteins M2 and M1, while the center of the viral particle contains the ribonucleoprotein complex (segments of viral RNA and polymerase basic protein 1, polymerase basic protein 2 [PB 2], and polymerase acidic protein [PA]), nucleoprotein (NP), nuclear export protein, and non-structural protein 2. The genome consists of a single-stranded RNA chain with 8 segments, which produce between 8 and 12 viral proteins.[11–16]

Viral Cycle

The influenza virus anchors on the host cell when HA binds with the sialic acid of the glycoproteins or glycolipids on the cell membrane.[17] The influenza species affecting humans selectively recognize the sialic acid linked to galactose by a α2,6 (SA α2,6Gal) linkage abundant in the epithelial cells of the respiratory tract.[18,19] Once the virus binds to the membrane receptor, it enters the host cell by a process of endocytosis. It is released into the cell cytoplasma, and its membrane is fused to that of the endosome. Viral HA plays a key role in this process, because when it is cleaved by the host proteases[20,21] a region known as "fusion peptide" is exposed. This interacts with the endosome membrane, resulting in the fusion of the membranes and the release of the contents of the virion into the cell cytoplasm.[22–24] An important step in this process is endosome acidification which is mediated by the M2 ion channel protein. Protons enter through this channel and cause the M1 matrix protein to dissociate from the ribonucleoprotein complex of the virus, which is then released to the cytoplasm for subsequent nuclear importation.[25–27] Once inside the nucleus, viral RNA is transcribed to messenger RNA (mRNA), which then undergoes the polyadenylation essential for the expression of viral proteins.[28] Viral proteins are translated by the host cell machinery, and when the PA, PB and NP proteins have been synthesized,