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A Review: Influenza and its Therapeutic Approaches

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ABSTRACT

The high degree of variability amongst influenza viruses is the main characteristic that provides the greatest challenge to development of prophylactic and therapeutic solutions against epidemic and pandemic outbreaks. Therapeutic treatment option for pandemic, seasonal and zoonotic influenza viruses are antiviral neuraminidase inhibitors. Currently neuraminidase inhibitors, such as oseltamivir, zanamivir, laninamivir, and peramivir can be used as potential drug use for treatment for H1N1 in different countries [1, 2] but due to some controversies and emerging in resistance the effectiveness of such drug decreases. In this review article we focus on different aspects for treatment such as Monoclonal antibody, Sialic acid inhibitor and universal influenza vaccine. In the past decade, more focus will be on universal influenza vaccine for treatment which provides the long lasting effect on multiple subtype of flu rather than particular type of flu, such vaccine can provide the protection against seasonal and newly emerging flu viruses and based on relatively conserved sequence and protein of influenza viruses.

KEYWORDS: Neuraminidase, Monoclonal antibody, Influenza, Sialic acid universal vaccine

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INTRODUCTION

Virus Structure

Influenza H1N1 is the orthomyxovirus single strand RNA virus with size 80 to 120 nm in diameter which is highly contagious pathogen and most common cause of worldwide pandemic outbreak in2009[3].H1N1 influenza virion is roughly spherical and enveloped virus the outer layer is lipid membrane with inserted spikes, which are actually the glycoprotein linked with the sugar known as heamagglutinin and neuradiminase which describe the subtype of influenza. The influenza virus is single strand RNA genome with eight segment which encode 11 different proteins such as enveloped protein HA and NA, viral RNA polymerase includes PB1, PB2 and PA., matrix protein M1 and M2 and non-structural protein NS1 and NS2[3, 4]. Influenza Avirus subtype, is contagious disease spreads from person to person by coughing and sneezing or by droplet infection categorized into three groups: influenza A, influenza B, and influenza C. The most common cause of disease in humans is from influenza A viruses, which are further classified into strains based on their Surface proteins HA and NA (Heamglutina Neuradiminase) present on the viruses so strains of influenza are named things like H3N2 or H1N1. These strains shift evolved over time, called as antigenic shift due to which that there is new strain evolves every year with different antigenic characters, slight in the genetic structure of strain lead to seasonal outbreaks, whereas a big change in the virus can lead to huge worldwide outbreaks known as pandemics.

Neuraminidase inhibitors for controlling of influenza infection:

Influenza A viruses is the most harmful and pestiferous virus belongs to Orthomyxoviridae family. The influenza A virus genome encodes, apart from hemagglutinin and neuraminidase, ion channel (M2), matrix protein (M), nucleoprotein (NP), RNA polymerase components, and non-structural proteins, viruses can be classified based on different antigens present on the surface of virus. The genetic variability of influenza viruses is caused by the frequent occurrence of point mutations in the hemagglutin in and neuraminidase genes and by occasional genetic rearrangements between different viruses from humans and animals [5].The viral neuraminidase and hemagglutin in bind to the terminal sialic glycocalyx acid residues of the host cell surface. Binding of hemagglutin in to sialic acid is necessary for viral internalization by the host cell and Neuraminidase then cleaves the sialic acid linking the viral hemagglutin in and cell surface glycans, liberating newly formed virions and maintaining the cycle of infection[6]. Three inhibitors have been developed based on sialic acid: zanamivir; its ethyl ester derivative oseltamivir; characterized by improved bioavailability; and peramivir, which was first used for treatment of hospitalized and paediatric patients [6, 7, 8, 9]. All neuraminidase inhibitors were shown to be effective only if administered no later than 36–48 hours

after first manifestation of the symptoms[10]. According to a recent estimation, ~99% of seasonal influenza viruses are sensitive to all licensed inhibitors and thus making these drugs an appropriate choice for influenza treatment [11].

Monoclonal Antibody as therapeutic approach:

The high degree of variability among the influenza virus is the main characteristic that provides the greatest challenge to development of prophylactic and therapeutic solution against the epidemic and pandemic outbreak. in particular the current antiviral vaccine and drug cannot confer the complete protection against circulating virion and hence new approaches are develop such as monoclonal antibody, antibodies are glycoproteins of the immunoglobulin super family and produced by plasma cell which is derived from differentiated B lymphocyte from of the immune system Monoclonal antibodies are effective and targeted approach and continue to be growing class of drug in the past decade due to their high degree of specificity and safety [12,13,14]. number of human monoclonal antibodies have been described that can bind to and neutralize a broad range of influenza A and B viruses. Heamglutinin is an important target of these monoclonal antibodies effects are developed to produce the broad spectrum antibody anti-HA stalk antibody that recognize the conserved structure in the membrane of stalk domain of heamagglutinin and some have been evaluated in the early to mid-stage of clinical trial [14,15,16]. An important conclusion from these clinical studies is that hem agglutinin stalk-specific antibodies are safe and can reduce influenza symptoms.In the Future, antibody-based therapies might become important part for treatment of influenza virus and have been found to inhibit virus replication. Importantly, most monoclonal antibodies that target the globular head of heamglutinin bind and neutralize conserved epitopes in HA have been developed, and these antibodies show promise as inhibitors of many different influenza virus strains [17,18].

Influenza vaccine uses as therapeutic approach:

Vaccination is an effective approach for the control and prevention of influenza. Currently, trivalent inactivated-virus (TIV) flu shot injection vaccines against seasonal influenza viruses are the most frequently used influenza vaccines [19, 20]. TIV vaccines are composed of three influenza-virus strains (2 A subtypes, H3N2, H1N1, and 1 B type) selected primarily on the basis of forecasted prevalence during the targeted influenza season. QIV vaccines include the second B lineage [16]. TIV vaccines come in three different formulations; the whole virus, split virus, and submit. Both these vaccine were used for treatment of different seasonal influenza viruses there are three Method of production of influenza vaccine approve by US food drug and administration (FDA).

Egg-Based Flu vaccine -

The Most common way of production of vaccine as egg-based manufacturing process done by cultivating the virus in chick embryo and allow the virus to replicate in the chick embryo and after the virus containing fluid is harvested from the egg and virus antigen is purified In studies vaccine appears effective and safe providing strong effective immune response against seasonal influenza.

Cell Based Flu Vaccine –

It is cell based production of process of flu vaccine, this method of production of vaccine does not require the chicken egg for culturing the virus in this process virus are cultivated in animal cell for infinite for production of cell line. Cell culture technology has the potential for a faster start-up of the flu vaccine manufacturing process. The process of creating cell-based flu vaccines involves several steps the viral strain will replicate using the mammalian cells. Next, the virus is extracted from the cells in the liquid culture, purified, then tested or modified for the specific vaccine being produced.

Recombinant Flu Influenza

The third technology approved by FDA for production of vaccine involves the recombinant DNA technology to isolate a certain gene (hem agglutinin HA) from the wild type of virus and this gene is inserted into the vector and allow to replicate in the cells and the flu HA protein is harvested from these cells and purified and approved from FDA.

Leading Universal Influenza vaccine strategy:-

Influenza virus causes notable morbidity and mortality worldwide every year[21]. Vaccination is the most effective way to reduce clinical cases of influenza but frequent genetic shift and drift among the influenza strains limit the effectiveness of the available conventional influenza vaccine[22]. One approach to overcome this limitation is to develop the universal influenza vaccine that provides the protection against all the subtype of influenza virus, novel Antibody based universal influenza vaccine should be devised that provide the broad-spectrum of protection this include anti HA stalk, HA globular head and Influenza A M2E the matrix protein it is integral trans membrane protein of influenza virus A[24]. It has been reported these antibodies will provide important tools for antibody guided vaccine design but can also be used as therapeutics. The segmented genome of influenza virus can encode 11 viral proteins, providing several possible targets against which influenza vaccine could be employed[23]. Glycoprotein present on the surface of the of influenza virion can be easily

recognized by the the immune system and critical to the virus life cycle and sustainable efforts are made to target this protein.

M2E Based vaccine – The matrix protein are transmembrane proton ion channel involved in virus un coating and following entry[18-24]. An amino acid amino acid region of the protein that extend outward from the surface of virion is highly conserved among influenza A strain and that can be used as target for universal vaccine design.

Heamagglutin in Based Vaccine – Current flu vaccine induce the production of antibodies that recognize the heamagglutin in head of HA protein and inhibit its activity to mediate the viral entry into the cell, however this portion of protein may undergoes the rapid mutation to escape this ,the heamagglutin in stalk is far more resistant to mutation provide the target to antibody that block its activity that it may considered as universal vaccine Universal influenza vaccines are designed to generate antibodies that recognise conserved epitopes on the influenza virus surface. They are supposed to protect against more than one virus strain, and consequently for more than one season, potentially eliminating the need for annual immunizations. The development of such vaccines is underway, with the most advanced candidates in Phase III being Biondvax's M-001 and Medicago's MT-2271, and a new entry is the National Institutes of Health's (NIH's) H1ssF_3928.

CONCLUSION:

Currently neuraminidase inhibitors, such as oseltamivir, zanamivir, laninamivir, and peramivir can be used as potential drug use for treatment for H1N1 in different countries but due to several factors, such as drug effective dose, synergistic or antagonistic relations with other drugs, safety, and patient's resistance , identification of novel monoclonal antibodies and influenza vaccine are modern and evolving and adapting technology used for treatment of influenza infection scientist will be on search for novel universal vaccine which can provide the long lasting effect on multiple subtype of flu rather than particular type of Flu such vaccine can provide the protection against seasonal and newly emerging flu viruses .Vaccine is based on relatively conserved sequence and proteins of influenza viruses In addition to these vaccines, therapeutic mAbs that have the same conserved targets are developed in the clinic and show great promise as a future tool to combat influenza virus infections, so next coming year will be exciting time as vaccine based on stem and globular head of HA move from pre-clinical to clinical trial and these clinical studies would represent the effectiveness of this drug against the influenza strain over commercial available vaccine.

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