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CORRESPONDENCE ARTICLE

The role of neuraminidase inhibitors in the treatment and prevention of influenza

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The causative agents of acute respiratory infections in children and adults are mostly thought to be viruses. Many types of viruses could cause similar symptoms of ARI. Among them, influenza viruses A and B and respiratory syncytial virus (RSV) are thought to be the most important because of the severity of illness after infection and their high communicability in the human population [1]. Type C influenza virus usually is not serious and typically not included in discussion about influenza infection [2]. In this article, discussion is limited to influenza A and B only. These viruses belong to the orthomyxoviridae family of viruses [3].

Influenza infects an estimated 120 million people in the United States, Europe, and Japan each year and is a major cause of morbidity and mortality. In periods of flu pandemics, infection rates could be even higher. In the United States, out of an estimated 20 million cases of flu each year, up to 40 000 Americans die, and more than 400 000 are hospitalized. The resulting economic burden has been estimated to be as high as $12 billion. In the last few years, new developments in the prevention, diagnosis, and treatment of influenza have been introduced that will change the clinical milieu in the new millennium.

The traditional vaccine approaches to the prophylaxis have been problematic owing to the ability of these viruses to undergo antigenic shift by exchanging genomic segments or by undergoing antigenic drift, consisting of point mutations in the surface glycoproteins haemagglutinin (HA) and neuraminidase (NA) genes as a result of an error-prone viral polymerase. Antigenic shift is seen only in influenza A viruses and occurs when a novel HA or NA subtype is introduced from an animal influenza virus reservoir into the human population. Antigenic drift occurs in influenza A and B in and around the antibody binding site. Therefore, the annual update of influenza is necessary because of the annual occurrence of antigenic drifts. For example, for the 1999–2000 season, it was recommended that vaccines contain an A/Sydney/5/97 (H3N2)-like virus, an A/Beijing/262/95 (H1N1)-like virus, and a B/Beijing/184/93-like virus or B/shangdong/7/97-like virus. However, significant morbidity and mortality were clinically observed during this season, and indicated the obvious limitations of this method of prevention. As a result of these ongoing observations, other prevention and treatment modalities have been investigated and some have already been introduced to practice. The most recent breakthrough in that direction is the introduction of neuraminidase inhibitors for the treatment and prevention of influenza infection.

The neuraminidase is a surface glycoprotein that is composed of eleven conserved residues [4] which catalyze the cleavage of sialic acid residues terminally linked to glycoproteins and glycolipids and plays an important role in the replication of the virus. A recent new study demonstrated that Tyr409 is the most critical residue for enzyme activity, and that Asp149, Arg223, Glu275, and Arg374 also play important roles in enzyme catalysis [2]. Neuraminidase function is critical for the spread of virus to new cells, and if the enzyme activity is inhibited, then virus infection is abrogated [2, 5]. Also, there is evidence that this enzyme plays some role in the introduction of apoptosis to the infected cells [6].

Currently, there are two neuraminidase inhibitors (NI) available for clinical use: zanamivir and oseltamivir. In phase II trials (NAIB2005 and NAIB2008), benefit was seen in early treatment (within 36 hours of onset of illness). Virological substudies showed mean reductions in virus shedding after 24 hours of treatment of 1.5 to 2.0 log [10] 50% tissue culture infective doses compared with a placebo, with no reemergence of virus after completion of the therapy [7, 8]. In phase III trials, median times to alleviation of major symptoms were reduced by up to 2.5 days after treatment. Benefit of treatment in terms of time to return to normal activities, reductions in consumption of acetaminophen, and the reductions in the level of interference of influenza with sleep, work, leisure, and recreational activities were reported [9].

In the prophylaxis trials, statistically significant reductions in the incidence of influenza A was reported with the use of inhaled zanamivir in a double blind study that included 1107 persons in two university communities [9, 10]. In this study, zanamivir was 67% efficacious in preventing laboratory-confirmed clinical influenza and 84% efficacious in preventing laboratory-confirmed illnesses with fever. Also, intravenous zanamvir (600 mg twice daily for 5 days) used 4 hours prior to intranasal inoculation with infectious doses of influenza A virus was successful in reducing the frequency of viral shedding (0% *versus* 100% in placebo), seroconversion (14% *versus* 100% in placebo), fever (14% *versus*

88% in placebo), upper respiratory tract illness (0% *versus* 100% in placebo), and total symptom score (1% *versus* 44% in placebo) [11]. Another trial showed that outbreak of influenza A and B were prevented in a nursing home community [9].

Oral administration of oseltamivir (GS4104) in two randomized trials (1559 subjects given 75 mg once or twice daily) [12] reduced the risk of infection during the influenza season from 4.8% in placebo to 1.2% and 1.3% in the treatment groups. The protective effects of the drug were 74% in all study sites combined and 84% in the areas where the rate of influenza was higher. Another smaller study reached similar conclusions [13].

The coadministration of NI with inactivated trivalent influenza vaccine was investigated in England. It was found that it does not adversely affect the production of antihaemagglutinin antibodies in the serum [14]. Finally, although fighting influenza seems like boxing a heavyweight champion and odds are you will end up flat on your back, but with proper precautions and the development of new drugs you may be able to avoid getting knocked out.

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