business trends

Influenza therapies: vaccines and antiviral drugs

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Every winter those vulnerable and likely to be affected by influenza are offered the chance to be vaccinated; however, each year, controversy surrounds this issue, whether it is over who has the right to be vaccinated, questions over the drug manufacturer's ability to supply enough vaccine when it is needed, or the extra pressures of the predicted avian-flu crisis. With an increasing emphasis on the treatment and prevention of influenza, it is hardly surprising that drug companies are racing to get the next successful flu vaccine approved at a time when the rewards are huge, more money is being poured into researching this area and talk of compulsory generic licensing threatens those not seen to cooperate.

The influenza virus affects all age groups, although mortality in nonpandemic years is concentrated in the elderly. In temperate regions influenza spreads during the winter months resulting in acute respiratory infections. In certain vulnerable populations (the elderly, pregnant women, subjects with chronic disease and infants <2 years of age) contracting influenza can have very serious consequences. Even in otherwise healthy individuals, influenza contributes to loss of work hours and is a major contributor to hospitalization of children. The onset of influenza can be sudden, with the subject experiencing a fever, headache and other general aches, as well as the characteristic respiratory symptoms including cough, rhinitis and a sore throat.

Three types of the acute viral-disease influenza have been identified (types A, B and C), and the virus is further categorized according to the cell-surface proteins expressed: either hemagglutinin or neuraminidase.

The annual influenza epidemics are caused by types A and B; type C is not known to cause infection in humans. Type A is less stable than type B. Mutations in the viral genome cause the cell-surface proteins to be modified. Most mutations are minor, but the occasional major mutation can result in a new virus type. Influenza virus type A undergoes an antigenic change approximately every 30 years, which can result in a pandemic. Influenza type A has also shown the ability to cross the interspecies barrier. Influenza type B, however, is more genetically stable than type A and the epidemics it causes are generally much less severe.

One of the reasons influenza is such a concern is that it is particularly contagious. The virus spreads easily in the form of microdroplets produced when an individual coughs or sneezes. The virus can circulate rapidly in densely populated areas and in busy, enclosed environments such as schools and hospitals.

Vaccines

Vaccination is seen as the 'gold standard' in terms of influenza treatment because it not only decreases the risk of infection in the vaccinated individual, but also prevents the spread of the virus. The world market for influenza vaccines varies from US$1.1 billion to US$1.5 billion depending on the demand for the product. It is estimated that in 2004 the value of the seasonal influenza vaccine market was US$1.36 billion. Assuming the traditional influenza season for the next five years, it is estimated that by 2009 the market will have increased to US$3.6 billion [1].

Chiron vaccines is currently being acquired by the pharmaceutical giant Novartis. The acquisition of Chiron heralds the recent trend of big pharmaceutical companies buying into the vaccines business, and this investment will produce a more dynamic vaccines market as the effort to produce a universal vaccine continues.

Chiron produces four influenza vaccines: Fluvirin® (for the US market), Fluad®, Agrippal® (European market) and Begrivac® – a preservative-free formulation. It was announced in October 2005 that Chiron will produce the H5N1 avian influenza vaccine for a US government stockpile – to be used in the event of a pandemic.

Sanofi Pasteur, the vaccines division of Sanofi Aventis, currently produces Vaxigrip®, a split-virion inactivated vaccine intended to provide protection against the 2005–2006 influenza strains. Sanofi Pasteur is also working on a vaccine for the H5N1 strain to be used in a pandemic situation. This vaccine has just completed Phase I trials and was shown to be safe and well tolerated. Phase II results are expected in 2006.

Delivered as a nasal mist, MedImmune's Flumist® contains live, attenuated influenza virus reassorts of the strains recommended by the US Public Health Service for the 2005–2006 season.

GlaxoSmithKline currently manufacture a split-virion inactivated vaccine called Fluarix®, which is available in the USA and in the UK for the prophylaxis of influenza (a summary of influenza vaccines is displayed in Table 1).

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TABLE 1

A summary of influenza vaccines

Trade name	Company (licensed)	Year of launch	Country
Fluarix®	GSK	1996, 2002	France, then Italy, UK and Western Europe
Inflexal V®	Berna (Solvay)	1997, 2000	Italy, then rest of Europe
Fluvirin® Agrippal® Begrivac® Fluad®	Chiron		USA and Europe
Fluvax®	CSL	1997, 2004	Australia, then Sweden
Fluviral®	Shire	2001	Canada
Flumist®	MedImmune	2003	USA
Anflu®	Sinovac	2005	China

Because the vaccine area is currently experiencing such a surge of growth and promotion, there are many efforts worldwide targeted at antiviral drug discovery and vaccine development.

In October 2005, Australia's government-backed research funder, the National Health and Medical Research Council, pledged Aus$7.5 million for urgent research, including pandemic influenza research [2]. Also, Melbourne-based biopharmaceutical firm CSL has been granted Aus$4.93 million by the Australian Federal Government to fast-track pandemic influenza vaccine production. CSL has a deal with the Australian government to supply 65% of its influenza vaccine needs for the next three years.

In the USA, MedImmune will collaborate with the NIH to develop new pandemic influenza vaccines. Using MedImmune's reverse-genetics technology, versions of Flumist® will be produced and tested against different types of potential pandemic strains, including H5N1 [3].

A problem with current influenza vaccines is that they are not universal and, therefore, the formulation needs to be changed each year to tackle different strains. Acambis is hoping to overcome this with their debut into the world of influenza vaccine development by producing a permanent, universal vaccine [4]. Furthermore, an EU grant has been awarded to the Swedish company Arexis to support research into a nasally delivered vaccine offering lifelong protection from influenza [5].

Although vaccination remains at the forefront of influenza prevention, antiviral agents are clearly beneficial. Influenza antivirals have a use as a prophylactic treatment until a vaccine becomes effective. They can also be given to all high-risk individuals who are unable to take the vaccine. Another good example of a time when antivirals might have been relied on is the 2004–2005 influenza season, when the UK and USA were left to turn to other suppliers when Chiron's license to manufacture Fluvirin® in its Liverpool (UK) facility was suspended for three months. Chiron had to withdraw ~40 million does of Fluvirin® [1]. During this time the USA had Fluzone® and FluMist® provided by Aventis Pasteur (now Sanofi Pasteur) and MedImmune, respectively.

Because of the nature of vaccine preparation in the event of an influenza pandemic (i.e. there is likely to be a six month lag time between identifying the strain causing the pandemic and developing a suitable vaccine), the availability of antivirals is crucial to ensure that some treatment is available within this time – to help manage the early stages of the pandemic. Also, antiviral agents are more effective if they are given in the early stages of infection and are not strain-specific; therefore, they are effective against different strains of the virus.

Antivirals

The status of drugs in development with influenza as an indication is shown in Figure 1. Two of the drugs, oseltamivir and zanamivir, share the same pharmacology; they are both neuraminidase inhibitors, which are considered to be a significant advance in antiviral drug development because of their high efficacy, good safety profile and low levels of resistance. Neuraminidase inhibitors prevent the dissemination of new viral particles by irreversibly binding to the sialic acid binding site of neuraminidase. Several studies have demonstrated the effectiveness of neuraminidase inhibitors for prophylaxis and treatment of influenza, and both drugs have been shown to reduce the duration of symptoms.

Zanamivir (Relenza®), first launched in 1999, was developed by Biota for the treatment and prevention of influenza A and B. It is now

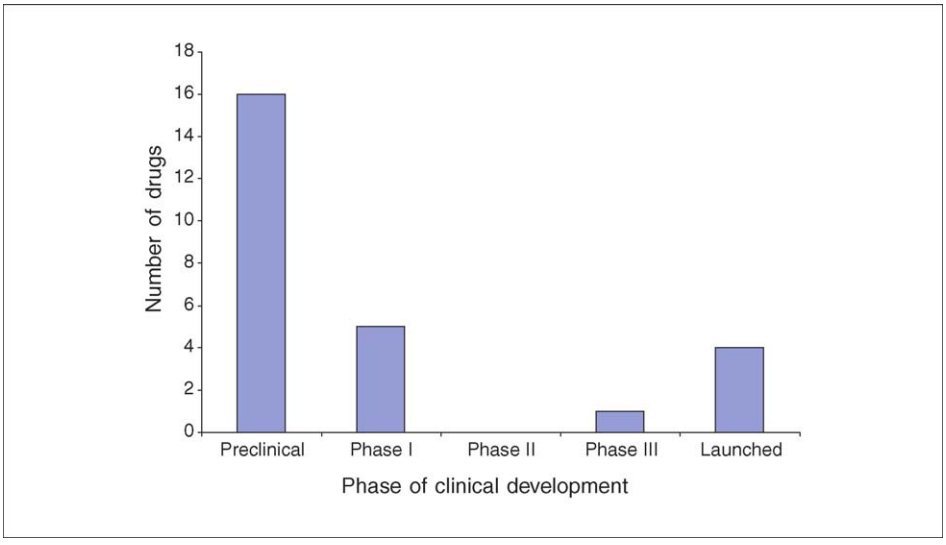

FIGURE 1

Drugs in active R&D. The number (and status) of drugs in R&D that treat influenza. Figure reproduced, with permission, from Pharmaprojects.

licensed to GlaxoSmithKline and is administered by inhalation using GlaxoSmithKline's Diskhaler®. Oseltamivir is less expensive and is orally delivered, which suggests oseltamivir is the preferable option of the two neuraminidase inhibitors.

Oseltamivir (Tamiflu®), first launched by Gilead Sciences in 1999 and now licensed to Hoffmann-La Roche, has recently received publicity with regard to its possible use against the predicted H5N1 pandemic. In a recent review of oseltamivir, Professor John Oxford stated that the signs show an influenza pandemic is on its way and that 'planning through the stockpiling of appropriate agent(s), such as oseltamivir, is currently the most crucial single defence to be utilized against this virus' [6].

However, although it is generally thought that neuraminidase inhibitors are the best antivirals because of their efficacy and safety profile, there are concerns about their use in a pandemic situation. The ability to manufacture oseltamivir is limited when it is only licensed to one company, especially because the drug takes a year to produce. For enough oseltamivir to be produced in the time before a pandemic could hit, it needs to be sublicensed to other companies for manufacture and then stockpiled by countries in great enough quantities to treat the infected population. In 2005 Hoffman-La Roche agreed to sublicense oseltamivir production to Hetero Drugs in India and Shanghai Pharmaceuticals. Roche is currently negotiating a sublicense with a company in China. Furthermore, recent reports have highlighted the occurrence of resistance to oseltamivir, yet no zanamivir-resistant strains have been isolated. It is thought this occurs because of a part of the chemical structure of oseltamivir that is not present in zanamivir.

Stockpiling of oseltamivir was initially recommended so that, in the event of an outbreak, it can be accessed immediately and used when it is most effective. However, the fact that oseltamivir has become so ubiquitous might have contributed to resistant strains developing. Also, if the general public have access to such a drug, it might be used incorrectly. If further development of resistant strains is to be prevented, oseltamivir must be prescribed in a controlled manner and patients must be educated so that it is only used in the correct situations.

Rimantadine, an adamantine, is another antiviral used for treatment and prophylaxis of influenza. It has a similar efficacy to the neuraminidase inhibitors and is less expensive; however, it has more adverse effects, particularly associated with the central nervous system.

Influenza antivirals could be seen to progress in the same way as antiretroviral drugs used for the treatment of HIV. Combination therapy using HIV antiretrovirals is now standard but a limited amount of research has been done into the effectiveness of influenza antiviral drugs in combination with one another.

There are many other agents that can be used to treat the symptoms of influenza, as well as the secondary complications; for example, Pfizer's Zithromax® (azithromycin). This macrolide antibiotic inhibits protein synthesis by reversibly binding to the 50S subunit of the bacterial ribosome, treating sinusitis and lower respiratory tract infection.

Conclusion

A continual problem with influenza treatment is the need to identify the dominant strains of influenza before the peak influenza season to develop a vaccine in time. Approximately six months are currently required to develop a vaccine and certain types of vaccine are known to be less effective at inducing protective immunity in young children and the elderly. Clearly, this is an area where further research is needed. The Holy Grail of viral vaccine development is to produce a vaccine that can induce heterosubtypic immunity (i.e. the host is protected against variant strains of the virus). Such a vaccine would be a massive breakthrough because it would mean there was no longer a need for yearly vaccination and would ensure protection against pandemic viral strains. Until this type of vaccine is more attainable, the focus of research is to develop a vaccine that is longer-lasting and provides stronger immunity to the vulnerable groups that need it most.

Antiviral drugs also have an important part to play in the battle against influenza and it is likely to be a combination of vaccines and antiviral agents that is needed to control the virus. However, a limitation of antivirals is that they often need to be given soon after the initial infection to be effective. A therapy that can be given at a later stage and still be as effective would be another achievement.

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