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Demystifying FluMist, a new intranasal, live influenza vaccine

ABSTRACT

FluMist—a cold-adapted, live-attenuated, trivalent, intranasal influenza virus vaccine approved by the US Food and Drug Administration on June 17, 2003—has been shown to be safe and effective, but its role in the general prevention of influenza is yet to be defined. Intranasal administration is expected to be more acceptable than parenteral, particularly in children, but the potential for the shedding of live virus may pose a risk to anyone with a compromised immune system.

KEY POINTS

The cold-adapted, intranasal vaccine elicits immunity in the cooler environment of the nasal passages, but does not grow well in the warmer environment of the lungs.

The efficacy of the live-attenuated vaccine against culture-confirmed influenza is 93% in children and 85% in healthy adults.

The most common side effects of the live-attenuated vaccine are transient rhinorrhea and sore throat.

Live-attenuated intranasal vaccine is easy to administer. It is indicated for healthy people ages 5 to 49. People who are immunocompromised or considered at high risk should not receive the live-attenuated vaccine.

In the future, the live-attenuated vaccine may be combined with inactivated vaccines for people who are not expected to respond adequately to either vaccine alone.

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NOW THAT A COLD-ADAPTED, live-attenuated, trivalent, intranasally administered influenza vaccine has US Food and Drug Administration (FDA) approval, questions remain about its exact role in clinical practice.

The current indications for FluMist (MedImmune Vaccines, Gaithersburg, Md), and the fact that it costs about seven times more per dose than parenteral inactivated vaccine, may limit its widespread application. Moreover, since people vaccinated with live-attenuated virus may shed live virus in their nasal secretions, we do not yet know what risk this will pose to our aging population and the growing number of immunocompromised patients.

FluMist's higher cost may be offset by its easier administration, which does not require medical personnel. More importantly, wide acceptance of the live-attenuated vaccine could result in higher rates of vaccination, better protection against influenza, and lower cost of caring for influenza-related complications.

In this article I will address these questions and try to put the new vaccine into clinical perspective.

THE EPIDEMIOLOGY OF INFLUENZA

Despite the development and widespread availability of inactivated influenza vaccines, annual influenza-associated deaths have increased significantly over the last 3 decades, reaching about 65,000 in the 1998-1999 influenza season.[1] Influenza-associated hospitalizations in the United States range from 16,000 to 220,000 per epidemic.[2] In one study,[3] 38% of household contacts of cases of influenza (children accounted for most index cases) developed clinical influenza.

The 2002-2003 season was mild,[4] but this is no reason for complacency. The burden of illness of the annual influenza epidemics, the 1997 Hong Kong avian influenza A (H5N1) epidemic and threatened pandemic, and (as of this writing) the avian influenza A (H7N7) epidemic in the Netherlands should all reinforce the importance of our efforts to prevent and treat this infection.

INACTIVATED VACCINE: PLUSES AND MINUSES

Numerous studies have shown that the currently available parenteral, trivalent, inactivated influenza vaccine is cost-effective and efficacious in healthy working adults[5] and the elderly.[6] Economic evaluation of strategies for the control and management of influenza have clearly shown superiority of immunization over both chemoprophylaxis and early treatment.[7]

Unfortunately, influenza vaccine is still underused, and unless more measures are taken to facilitate immunization, it will be difficult to achieve the national health objective for 2010 of vaccinating at least 90% of the population over age 65.[8]

FluMist is approved for healthy people ages 5 to 49 only

The inactivated vaccine has been shown to be very safe. However, recent data have raised concerns about mild ocular and respiratory symptoms attributable to the split (trivalent) influenza vaccine.[9] In addition, it does not induce a local antigen-specific immune response in the nasal mucosa, which may explain its suboptimal efficacy in certain groups of patients.[10]

HISTORY OF THE LIVE-ATTENUATED VACCINE

The Russians have been developing the cold-adapted, live-attenuated influenza vaccine over the last 3 decades.[11] In the United States in 1967, Dr. Maassab from the department of epidemiology at the University of Michigan School of Public Health developed a cold-adapted virus that bred well in nasal passages and did not mutate to more dangerous forms.[12] The process involved gradual lowering of the temperature in which the virus grows, through a series of stepwise passages, resulting in a mutated, weakened virus that does not grow well at the higher temperature of the lungs but does replicate in the nasal passages, eliciting local immunity.[13] Dr. Maassab used these mutant viruses in genetic reassortment to produce different types of cold-adapted and wild strains in order to update the relevant surface antigens of the circulating strains of influenza virus.

COMPARISON OF LIVE-ATTENUATED AND INACTIVATED VACCINES

FluMist, marketed by MedImmune and Wyeth Pharmaceuticals (Madison, NJ), is a trivalent vaccine containing two influenza A strains and one influenza B strain, as in the trivalent inactivated vaccine. Intranasal administration has potential advantages over parenteral administration. The intranasal live-attenuated vaccine induces nasal mucosal influenza-specific immunoglobulin A (IgA) to the hemagglutinin of each of the three components of the vaccine,[14] which is advantageous because the nose is the portal of entry of influenza virus.

Even though live-attenuated vaccine induces significantly lower levels of serum hemagglutinin-inhibiting antibody than does inactivated vaccine, a large meta-analysis that included 18 randomized comparative clinical trials involving 5,000 vaccinees of all ages showed them to be equally efficacious in preventing culture-positive influenza.[15] Another large comparative study conducted over 5 years showed that the inactivated vaccine was slightly more efficacious than the live-attenuated vaccine in preventing influenza A (H3N2) disease (74% vs 58%, respectively), but the opposite was true for influenza A (H1N1) disease (76% vs 85%, respectively).[16]

Yearly vaccination with the live-attenuated vaccine continues to induce high antibody titers, with higher titers detected in those immunized for the first time.[17]

EFFICACY OF THE LIVE-ATTENUATED VACCINE

The efficacy of a live-attenuated vaccine against serologically and virologically confirmed influenza virus infection in Russian studies is 94% in children, and the efficacy of

combined inactivated and live-attenuated vaccines in the elderly is estimated to be 68%.[18] Similar findings have been confirmed in US studies of children and adults.

In children

In a study of 1,602 children, the vaccine's efficacy against culture-confirmed influenza was 93%.[19] One dose was almost as effective as two doses (89% vs 94% efficacy, respectively). In addition, vaccinated children had fewer febrile illnesses, including 30% fewer episodes of febrile otitis media. Serologic response, however, seems to be age-dependent, with lower response in children younger than 6 months, who have an underdeveloped immune system.[20]

The attenuated viruses are expected to replicate readily in children not previously exposed to influenza viruses, thus providing a higher efficacy than in previously infected adults.[21]

In adults

The estimated protective efficacy of the live-attenuated vaccine in healthy adults challenged with wild-type influenza A and B viruses was 85%,[22] with a range of 23% to 100% in one meta-analysis.[15] The corresponding range in the elderly population is 51%[23] to 61%.[24] In healthy, working adults, the vaccine reduced the number of severe febrile illnesses by 18.8%, febrile upper respiratory tract illnesses by 23.6%, days of work lost by 17.9%, days with health care provider visits by 24.8%, use of prescription antibiotics by 47%, and use of over-the-counter medications by 27.6%.[25]

Additional potential benefits

Interestingly, the vaccine provided substantial cross-protection against a variant influenza A virus strain in a year of poor matching between the type A (H3N2) vaccine strain and the predominant drifted circulating virus strain.[25,26]

Economic analysis has shown that the vaccine would be cost-saving in children when administered in a group-based delivery scenario, but not in an individual-based scenario, if its cost was under $28,[27] and in healthy, working adults if the cost was about $39.[28]

SAFETY OF THE LIVE-ATTENUATED VACCINE

Several studies have shown the live-attenuated vaccine to be safe.

Side effects in children were transient and included rhinorrhea, nasal congestion (48%), irritability (27%), decreased activity (13%), fever (12%), vomiting (6%), muscle ache (3%), and abdominal pain (2%), observed primarily with the first vaccine dose.[19,26,29] Adult vaccinees were more likely than placebo recipients to experience runny nose (44%) or sore throat (26%) during the first 7 days after vaccination, but serious side effects were not significantly different.[25]

In people with asthma, HIV infection

The vaccine is relatively well tolerated in children and adolescents with moderate to severe asthma.[30] Studies also found the vaccine to be safe and well tolerated in asymptomatic children and adults infected with human immunodeficiency virus (HIV).[31,32] No significant changes were seen in HIV RNA concentrations, CD4 counts, or CD4%, nor was prolonged or increased shedding of the influenza virus vaccine strain seen. This suggests that if a previously undiagnosed HIV-infected person receives the vaccine, significant clinical consequences are unlikely.

Side effects in the first week included runny nose (44%) and sore throat (26%)

In the elderly

People age 65 and older with chronic cardiovascular or pulmonary conditions or diabetes mellitus who were given live-attenuated vaccine in addition to inactivated vaccine developed sore throat more frequently than placebo recipients during the 7 days after vaccination, but otherwise they tolerated the vaccine well.[33]

Risk of gene reassortment

One concern is the biological risk inherent in the large-scale use of infectious influenza virus, with the chance of gene reassortment with non-human influenza virus strains, giving rise to new viruses of unknown virulence.[15,34] However, since common internal genes for attenuation are present in the vaccine, this would safeguard against reversion to virulence.[34] It is reassuring that phenotypic and molecular stability in this vaccine's reas-

sortants has been demonstrated in a very large number of patients, both in Russia and the United States, without clinical evidence of reversion to virulence.[34]

HOW TO USE THE LIVE-ATTENUATED VACCINE

Candidates

FluMist is intended for people ages 5 to 49 years. It is not approved for those under age 5 years or over age 49. Other contraindications include asthma, chronic cardiovascular or pulmonary conditions, pregnancy, diabetes, renal dysfunction, hemoglobinopathies, and immunocompromised states. Those who receive FluMist should avoid close household contact with immunocompromised people for at least 21 days. The risk of viral shedding and transmission of the weakened virus to such people is not yet known. Giving this vaccine to health care providers would be problematic.

Egg allergy

As with inactivated vaccine, use of live-attenuated vaccine is contraindicated in patients allergic to eggs.

Intranasal administration can be done in a variety of nonmedical settings

Dosing

Children ages 5 to 8 will need two doses at least 4 weeks apart in their first year of influenza vaccination with FluMist, and people ages 9 to 49 need only one dose. The dose is 0.25 mL administered in each nostril, supplied as premixed syringes.

Proper storage

Since the vaccine is preserved only by freezing, it must be used within 24 hours of thawing. This may complicate its distribution, storage, and use in large vaccination campaigns.[21]

Thimerosal

FluMist does not contain thimerosal, the mercury-containing compound often used as a preservative in inactivated influenza vaccine. Only a limited amount of the parenteral inactivated vaccine with reduced thimerosal is being prepared for the 2003-2004 influenza season[2]: Wyeth and MedImmune have indicated that they will make only 4 million doses available for the 2003-2004 season. Wyeth has discontinued the making of inactivated influenza vaccine in anticipation of the approval of its live-attenuated vaccine.

INTRANASAL ROUTE MORE ACCEPTABLE

The intranasal live-attenuated vaccine is expected to have a much better acceptance rate among children compared with the parenteral vaccine. It therefore has the potential to significantly reduce the transmission of influenza among families and, subsequently, could reduce the burden of illness in the community.[16,35] It is estimated that mass vaccination of 70% of children with this vaccine could provide substantial protection to the whole community.[36]

Since nasal administration of this vaccine could be taught to adults with no prior medical training, one can envision its delivery in the work setting, schools, day care centers, and at home. Enhanced compliance could present a new preventive strategy for employers and managed care organizations.[37] It may also have a role in the event of an influenza pandemic.[18]

COST

FluMist costs $46 per dose, compared with $6.25 for the inactivated vaccine. Cost-effectiveness data should be reevaluated in this context.

FUTURE DIRECTIONS

Influenza immunization rates have reached a plateau during the last few years. Clearly, more patient and physician education is needed, both to recommend vaccination and to counter myths about its adverse reactions.[38]

An intranasal *inactivated* vaccine for people age 50 and older

Since the live-attenuated vaccine is not recommended for people over age 49, other measures to improve vaccination rates and the protective response of vaccination in this age group are needed. A study from Israel has found an intranasal inactivated influenza vac-

cine more effective than parenteral inactivated vaccine in inducing mucosal IgA response in community-dwelling elderly people.[39] Another study comparing both vaccines in nursing home residents who were mostly elderly showed live-attenuated and inactivated vaccines to be of equal clinical efficacy (51% vs 50%, respectively).[23]

Combination vaccine

Several studies have shown additional protection attained by combining the inactivated parenteral vaccine with the live-attenuated intranasal vaccine.[23,24,33,40,41] This combination enhances both local and systemic immune responses against influenza,[40] potentially correcting the age-dependent weakening of the immune response to vaccination,[41] thus providing a strategy for improved influenza vaccination in the elderly, including nursing home residents[23,24] and those with underlying chronic medical conditions.[33]

Other proposed designs for influenza vaccine include genetically engineered live vaccines, vaccines expressing altered NS1 genes, "replication-defective" vaccines, DNA vaccines, and novel adjuvant agents.[42,43] The possibility of developing a universal influenza vaccine remains elusive due to the annual antigenic drift in influenza viruses. Unfortunately, the conserved parts of the influenza virus, the minor antigens, are less immunogenic and thus are unlikely to induce a protective response.[42]

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