Neuraminidase inhibitors take bite out of influenza

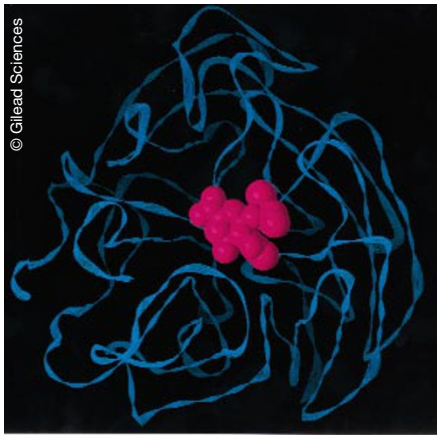
Neuraminidase inhibitors (NIs) will "change the picture" of how we treat flu, predicts Arnold Monto, professor of epidemiology at the University of Michigan School of Health (Ann Arbor, MI). Phase III data for zanamivir (Relenza), an inhaled drug developed by Glaxo Wellcome (London), and GS4104, an oral flu drug developed jointly by Hoffmann-La Roche (Basel, Switzerland) and Gilead Sciences (Foster City, CA), suggest this new class of drugs is effective at reducing the duration and severity of influenza, as well as at reducing the frequency of complications and associated antibiotic use. The estimated annual market for NIs as flu treatments is around $700 million, a figure that could increase significantly with prophylactic use of the drugs.

Influenza affects approximately 120 million people in the United States, Europe, and Japan each year, and is responsible for 20,000 to 40,000 deaths annually in the United States alone. Current treatments have limited effectiveness and work against type A influenza only. The nasty neurologic side effects mean they are rarely used for prevention, and typically only in high-risk individuals. In addition, resistant viral strains begin to appear within a couple of days of treatment, posing a significant risk in closed communities.

NIs block viral replication by targeting a site on one of the two main surface structures of the influenza virus, preventing the virus from infecting new cells. Zanamivir was one of a group of molecules developed by GlaxoWellcome and academic collaborators using structure-based drug design methods targeted at a region of the neuraminidase surface glycoprotein of influenza viruses that is highly conserved from strain to strain.

Monto, a lead investigator for Glaxo's prevention study, foresees greater acceptance of the NIs compared with the existing 30-year-old flu drugs, amantadine and rimantadine, because "we have a clear idea of how they work," they are equally effective at treating type A and B influenza, they have prophylactic capability if given early in the course of a flu pandemic, and they have virtually no side effects. Furthermore, early evidence suggests that viral resistance is not a problem.

The annual market for NIs to treat patients with influenza could exceed $700 million, according to Meirav Chovav, a biotechnology analyst at Salomon SmithBarney (New York). The overall market potential for these drugs climbs to several billion dollars if you take into account the large preventative market, he says.



Gilead's inhibitor (pink) binds active site of the neuraminidase enzyme (blue).

Both Glaxo and Roche presented phase III data at the Interscience Conference on Antimicrobial Agents and Chemotherapy, September 24–27 in San Diego, CA. Roche reported that GS4104 lessened the severity of flu symptoms by 25–40%, reduced the duration of illness by about 30%, and reduced secondary flu complications, such as bronchitis and sinusitis, by 50% in previously healthy adults.

Zanamivir, when taken within 36 hours of the symptom onset, relieved major flu symptoms 1.5 to 2.5 days sooner than placebo. Among patients at risk of developing complications, those given zanamivir had a 70% reduction in complications and a 61% drop in antibiotic use. Among patients in high-risk groups, treatment with NIs reduced the duration of flu symptoms from 8 days to 4 days, according to Monto. A phase III study of zanamivir in influenza prophylaxis (in type A viral infection only) showed that 67% of unvaccinated patients were protected from laboratory confirmed illness, as were 84% of patients who had fever as a presenting symptom.

Glaxo filed for marketing approval for Relenza in Europe and Canada in late September; Roche is expected to submit GS4101 for regulatory approval in the United States in 1999. Although the cost of these new drugs could affect prescribing practices, Chovav does not expect price to be a major issue, as the economic toll of flu and its complications is high.

In addition to the Roche and Glaxo drugs, BioCryst (Birmingham, AL) is developing preclinical NI compounds to treat influenza. In September, Johnson & Johnson (Fort Washington, PA) acquired exclusive worldwide rights to BioCryst's oral NIs in a deal valued at $12 million in up-front payments—$6 million in cash and $6 million in a stock equity investment—plus undisclosed milestone payments that could total $55 million. BioCryst reports that its lead compounds are effective for the treatment and prevention of influenza A and B in preclinical models. Pivotal trials are expected to start by winter 1999–2000.

Vicki Glaser

Vicki Glaser is a freelance writer working in Allentown, PA.

Future tense for in utero gene therapy

In September, French Anderson of the University of Southern California School of Medicine (Los Angeles), brought the issue of in utero gene therapy in the form of "preprotocols" before the once-tempestuous US National Institutes of Health (NIH; Bethesda, MD) Recombinant DNA Advisory Committee (NIHRAC). Although NIHRAC no longer issues recommendations to approve gene therapy research proposals, it remains a forum for airing public views on unusual proposals involving gene therapy. Anderson, a pioneer researcher and ethics conundrum poser in this field, says the procedures are at least three years away from testing in humans. The question of accidental introduction of genes into germline cells remains a major concern.

Partly based on their studies in sheep and mice, Anderson, Esmail Zanjani of the Department of Veterans Affairs Medical Center (Reno, NV), and their collaborators, describe detailed plans for in utero correction of two rare human genetic disorders: adenosine deaminase (ADA) deficiency, a metabolic defect that leads to severe combined immunodeficiency among children born with a defective ADA gene, and homozygous alpha-thalassemia, which stems from mutant alpha-globin genes and the deficient or missing proteins they specify.

Plans call for injecting corrective genes, carried on retroviral vectors, directly into the peritoneal cavity of fetuses during the second trimester of pregnancy (in the case of ADA deficiency) or into transiently withdrawn fetal blood cells (in the case of alpha-thalassemia). Fetal cells and tissues provide a milieu that poses fewer immunologic challenges to the injected genetic material than do those of a newborn or older individual, according to