EFFICACY AND SAFETY OF THE NEURAMINIDASE INHIBITOR ZANAMIVIR IN THE TREATMENT OF INFLUENZAVIRUS INFECTIONS

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ABSTRACT

Background The sialic acid analogue zanamivir (GG167) is a selective inhibitor of influenza A and B virus neuraminidases. These viral enzymes are essential for the release of virus from infected cells, and they may also reduce the inactivation of virus by respiratory secretions. When administered experimentally directly to the respiratory tract, zanamivir has potent antiviral effects. We assessed the therapeutic activity of zanamivir in adults with acute influenza.

Methods We conducted separate randomized, double-blind studies in 38 centers in North America and 32 centers in Europe during the influenza season of 1994–1995. A total of 417 adults with influenza-like illness of ≤48 hours' duration were randomly assigned to one of three treatments: 6.4 mg of zanamivir by intranasal spray plus 10 mg by inhalation, 10 mg of zanamivir by inhalation plus placebo spray, or placebo by both routes. Treatments were self-administered twice daily for five days.

Results Of 262 patients with confirmed influenzavirus infection (63 percent of all patients), the median length of time to the alleviation of all major symptoms was one day shorter (four days vs. five days) in the 88 patients given inhaled and intranasal zanamivir ($P=0.02$) and the 85 patients given inhaled zanamivir alone ($P=0.05$) than in the 89 patients given placebo. Among the infected patients who were febrile at enrollment and among those who began treatment within 30 hours after the onset of symptoms, the median time to the alleviation of major symptoms was four days in both zanamivir groups and seven days in the placebo group ($P\leq0.01$). Viral titers of nasal washings in the group given inhaled and intranasal zanamivir were significantly lower than those in the placebo group. The topically administered zanamivir was well tolerated.

Conclusions In adults with influenza A or B virus infections, direct administration of a selective neuraminidase inhibitor, zanamivir, to the respiratory tract is safe and reduces symptoms if begun early. (N Engl J Med 1997;337:874-80.)

TWO general measures are available to reduce the impact of influenza: immunization with inactivated vaccines and antiviral prophylaxis and therapy with amantadine and rimantadine.[1] The usefulness of amantadine and rimantadine is limited by an antiviral spectrum restricted to influenza A viruses, their uncertain effectiveness in severe influenza or in preventing complications, side effects, and the emergence of drug-resistant variants.[2] Consequently, there is a continuing need for more effective antiviral agents to manage influenza infections.

The sialic acid analogue zanamivir (GG167) is a potent, specific inhibitor of influenzavirus neuraminidase.[3,4] This enzyme, essential for replication in vitro,[5] cleaves terminal sialic acid residues from glycoconjugates to allow the release of virus from infected cells, prevent the aggregation of virus, and possibly reduce viral inactivation by respiratory mucus.[6,7] Zanamivir inhibits a range of influenza A and B viruses in vitro.[8,9] Topically applied zanamivir is active in animal models of influenza,[3,8,10] although systemically administered drug has little antiviral activity. In adults experimentally inoculated with influenza A virus, prophylactic intranasal zanamivir was highly protective against infection and febrile illness.[11] Treatment beginning one day after viral challenge also reduced peak viral titers by a factor of approximately 100 and reduced the frequency of febrile illness by 85 percent. We undertook studies to determine whether topical application of zanamivir would prove effective in the treatment of naturally occurring acute influenza. Because influenza commonly involves the lower respiratory tract,[12] both intranasal and inhaled forms of the drug were tested.

METHODS

Two parallel multicenter trials were conducted in North America (38 centers) and Europe (32 centers) during the 1994–1995 influenza season. Both were randomized, double-blind, and placebo-controlled in design and tested the same regimen of drug treatment.

Patients

Previously healthy persons who were at least 18 years old (at least 13 years in North America) with an acute influenza-like illness of ≤48 hours' duration during documented influenzavirus

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circulation in the community were enrolled. Illness was defined as the presence of fever and at least two other symptoms (headache, myalgia, cough, and sore throat). Suspected bacterial infection or recent use of antimicrobial drugs, immunization with influenza vaccine for the current season, pregnancy or breast-feeding, concurrent use of intranasal or inhaled medications, and underlying conditions for which influenza immunization is currently recommended were reasons for exclusion. Women of childbearing potential were enrolled if they were using an acceptable means of contraception and had a negative urine pregnancy test. Subjects provided written informed consent using a form approved by an appropriate institutional review or ethics committee.

Study Procedures

At enrollment, a medical history was obtained, a physical examination was conducted, and a complete blood count, blood chemical analyses, and urinalysis were performed. Serum for hemagglutination-inhibition tests (performed at the University of Rochester, N.Y., or the National Institute for Biological Standards and Control, United Kingdom) and nose and throat swabs or nasal washings for viral culture were also collected.

Patients were randomly assigned to receive one of three treatments: 10 mg of zanamivir by inhalation by mouth plus 6.4 mg by intranasal spray, 10 mg of zanamivir by inhalation plus placebo nasal sprays, or placebo by both routes. Treatments were self-administered twice daily for five days. A Diskhaler device (Glaxo Wellcome, Ware, United Kingdom) was used to administer two inhalations of a dry powder containing 20 mg of lactose and 5 mg of zanamivir by mouth. The aerodynamic mass median diameter of the micronized powder was estimated to be approximately 3.0 μM. Lactose alone served as the vehicle control. The nasal aqueous spray was administered as two 0.1-ml sprays per nostril. Compliance with the study medications was determined by having the patients keep daily diaries chronicling treatment. Each patient was given a package of relief medications, which included acetaminophen, dextromethorphan hydrobromide, and pseudoephedrine.

The patients recorded their symptoms (nasal stuffiness or runny nose, sore throat, cough, muscle aches, tiredness or fatigue, headache, loss of appetite, and feverishness) on a diary card each morning and evening. Severity was rated on a four-point scale in which a score of 0 indicated no symptoms, a score of 1 mild symptoms, a score of 2 moderate symptoms, and a score of 3 severe symptoms. Patients also recorded their oral temperatures twice daily and their ability to engage fully in usual daily activities. They returned one to three days after treatment for a follow-up examination, to provide laboratory samples, and to report any adverse experiences. They also returned during convalescence on days 21 to 28 for hemagglutination-inhibition antibody testing.

At three centers (Rochester, N.Y.; Charlottesville, Va.; and Winnipeg, Manitoba), nasal washings were collected on days 2, 4, 6, and 8 for titration of virus. Samples were frozen, and any that were initially culture-positive were cultured again in Madin–Darby canine-kidney cells to determine the median tissue-culture infective dose of virus ($\log_{10}$ $TCID_{50}$) per milliliter of sample.

Statistical Analysis

The primary clinical end point was the length of time to the alleviation of all major symptoms of influenza, as defined by the absence of feverishness and the presence of no other major symptoms (headache, myalgia, cough, and sore throat), or only mild ones, for at least 24 hours. For the analysis of this end point, the patients were grouped into 10 categories, from day 1 to day 10 or later, according to the day on which their symptoms resolved. Patients who withdrew with no evidence of alleviation of symptoms were included in the "day 10 or later" category.[13] Patients with influenzavirus infection, defined by the recovery of virus, a fourfold or greater rise in serum antibody titers on hemagglutination-inhibition testing, or both, were considered able to be evaluated in the efficacy analysis. All patients who received the study drug were assessed for adverse events.

The statistical-analysis strategy involved the combined use of nonparametric and model-based methods.[14] Pairwise comparisons of intranasal and inhaled zanamivir with placebo and of inhaled zanamivir with placebo were performed with an extended Mantel–Haenszel test, with integer scores stratified according to the protocol.[15] Estimates and confidence intervals for treatment effects were based on analysis of variance after allowance for effects due to the study protocol and treatment. The two tests were viewed as belonging to a hierarchy; no adjustments for multiple comparisons were made.

Prognostic factors identified as potentially influencing the efficacy of treatment included the study site (North America vs. Europe), the type of influenzavirus, the duration of symptoms before entry into the study, and the presence of fever at entry (oral temperature, $\geq$37.8°C). Tests of the interaction of each of these covariates with treatment were performed with analysis of variance. Where statistically significant interactions were observed, further subgroup analyses were performed.

Secondary end points included the lengths of time to the resumption of normal activities, to the alleviation of individual symptoms, to the loss of fever, and to the loss of detectable virus. The viral shedding area under the curve (AUC) was also determined.[11] The secondary end points were analyzed in the same manner as the primary end point, except for the viral shedding AUC, which was analyzed with analysis of covariance to allow for effects due to base line (day 1 value) and treatment. All analyses were performed with SAS systems and procedures.

Sample Size

The calculation of sample size was based on the assumption that major symptoms would be alleviated by the sixth study day in approximately 50 percent of influenzavirus-infected placebo recipients. A clinically relevant difference was defined as an increase in this fraction to 75 percent or greater. A sample of 195 infected patients (65 per group) is required for a two-tailed test of these proportions at the 5 percent level of significance and 80 percent power.[16] On the basis of an influenza-infection rate of approximately 70 percent, each study was designed to recruit 273 patients. However, neither individually reached its enrollment goal (111 infected patients in North America and 151 in Europe). Before the results were unblinded, we decided to perform a combined analysis of the two studies. The resolution of illness and effects of drug administration were similar in the two trials.

RESULTS

Patients

A total of 220 patients with suspected influenza were randomly assigned to a treatment group in North American centers and 197 in European centers (Table 1). Overall, 63 percent had laboratory confirmation of influenzavirus infection. The frequency of confirmed infection was higher in European centers (77 percent) than in North American ones (50 percent), in part because of the greater use of rapid antigen screening. Of the 262 influenza-positive illnesses, 56 percent were due to influenza A virus and 44 percent to influenza B virus. The predominant strains in North America were H3N2 subtypes, whereas influenza B infections predominated in Europe (Table 1). Most infected patients were culture-positive at entry; the duration of illness before enrollment averaged 31 hours in the three treatment groups. Other demographic characteristics of enrolled patients and their severity of illness were generally similar (Table 1), although an excess of

TABLE 1. CHARACTERISTICS OF 262 PATIENTS INFECTED WITH INFLUENZA ACCORDING TO TREATMENT CENTER AND TREATMENT GROUP.*

CHARACTERISTIC	NORTH AMERICA			EUROPE			COMBINED		
	PLACEBO (N=40)	INHALED ZANAMIVIR (N=37)	INHALED AND INTRANASAL ZANAMIVIR (N=34)	PLACEBO (N=49)	INHALED ZANAMIVIR (N=48)	INHALED AND INTRANASAL ZANAMIVIR (N=54)	PLACEBO (N=89)	INHALED ZANAMIVIR (N=85)	INHALED AND INTRANASAL ZANAMIVIR (N=88)
Type of infection — no. (%)†									
Influenza A	31 (78)	24 (65)	27 (79)	22 (45)	20 (42)	23 (43)	53 (60)	44 (52)	50 (57)
Influenza B	9 (22)	13 (35)	7 (21)	27 (55)	28 (58)	31 (57)	36 (40)	41 (48)	38 (43)
Culture positive — no. (%)	34 (85)	30 (81)	31 (91)	48 (98)	45 (94)	49 (91)	82 (92)	75 (88)	80 (91)
≥Fourfold increase in antibody titer — no. (%)‡	17 (42)	21 (57)	15 (44)	30 (61)	33 (69)	34 (63)	47 (53)	54 (64)	49 (56)
Male sex — no. (%)	22 (55)	24 (65)	22 (65)	26 (53)	26 (54)	28 (52)	48 (54)	50 (59)	50 (57)
Age — yr	31±14	29±12	30±13	35±11	32±10	34±11	33±12	31±11	32±12
Smoker — no. (%)	9 (22)	9 (24)	9 (26)	7 (14)	7 (15)	16 (30)	16 (18)	16 (19)	25 (28)
Duration of symptoms before study entry — hr	30±13	29±12	29±11	30±12	33±12	33±12	30±12	31±12	31±12
Symptom score at enrollment — % of maximal score§	61±16	60±16	60±16	58±19	57±18	60±18	59±17	58±17	60±17
Temperature, ≥37.8°C — no. (%)	28 (70)	23 (62)	19 (56)	26 (53)	23 (48)	32 (59)	54 (61)	46 (54)	51 (58)

*Plus–minus values are means ±SD.

†The presence of infection was defined on the basis of isolation of virus, an increase in antibody titer of fourfold or more on hemagglutination-inhibition testing, or both.

‡The hemagglutination-inhibition test was used to measure antibodies in serum samples.

§The score is expressed as a percentage of the maximal possible score of 24.

smokers was present in the group assigned to intranasal and inhaled zanamivir.

One patient randomly assigned to the placebo group failed to take the study drug. Eight other patients in the placebo group withdrew, as did 10 assigned to inhaled zanamivir and 10 assigned to inhaled and intranasal zanamivir. The most common reason for withdrawal was failure to return for the scheduled study visits.

The use of relief medications was common. The cumulative frequency of the use of acetaminophen (76 percent in the placebo group, 76 percent in the group given inhaled zanamivir, and 74 percent in the group given intranasal and inhaled zanamivir), cough medications (64 percent, 54 percent, and 52 percent, respectively), and decongestants (48 percent, 57 percent, and 40 percent) did not differ significantly during the treatment period.

Clinical Efficacy

For the 262 patients with confirmed influenza, the median time to the alleviation of major symptoms was five days in the placebo groups in both trials. This time was one day shorter in the groups assigned to inhaled zanamivir ($P=0.05$) and intranasal and inhaled zanamivir ($P=0.02$). By the third study day the proportion of patients whose illness was alleviated was higher in the zanamivir groups than in the placebo group, and this difference was maintained after the cessation of treatment (Fig. 1). No obvious differences were noted between the zanamivir groups.

Analysis of the intention-to-treat population revealed findings similar to those for the infected population, although the size of the treatment effects was smaller (Table 2). No evidence of benefit was observed in uninfected patients (data not shown). Further modeling analyses indicated that zanamivir was more effective in patients treated early, within 30 hours after the onset of symptoms ($P=0.02$ for the interaction with treatment), and in patients who were febrile at entry ($P=0.05$ for the interaction with treatment). There was no evidence of a difference in the treatment effect between type A and type B influenzavirus infections or between study locations (North America vs. Europe). Placebo recipients with documented fever on enrollment had more prolonged illness, and the median time to the alleviation of symptoms in this subgroup was two days longer than for the placebo-treated patients as a whole (Table 2). Among febrile patients who received zanamivir, symptoms were alleviated a median of three days sooner than in the placebo group ($P=0.01$ for the comparison of placebo with inhaled zanamivir; $P=0.001$ for the comparison of placebo with intranasal and inhaled zanamivir). In addition, the febrile zanamivir recipients resumed their normal activities a median of one day sooner than the febrile placebo recipients (Table 3). Those without fever on enrollment had no significant benefit of treatment (Table 2).

Among patients who were treated earlier in the course of illness (≤30 hours after the onset of symptoms), who represented half of the enrolled influenza-infected population, the administration of zana-

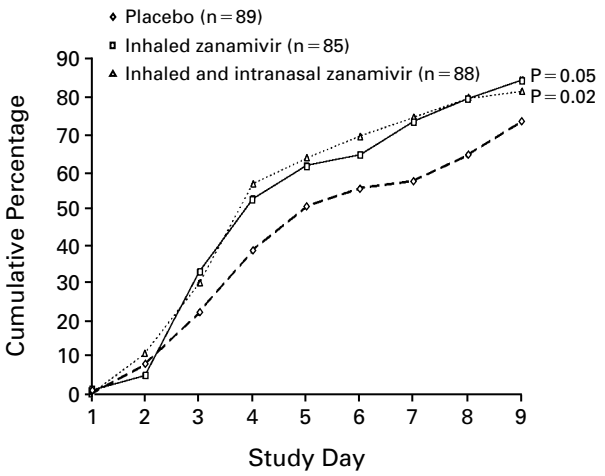

Figure 1. Alleviation of Symptoms in Patients Infected with Influenza A or B Virus Who Were Treated with Inhaled Zanamivir, Intranasal and Inhaled Zanamivir, or Placebo.

Alleviation of illness was defined as the absence of feverishness and the presence of no symptoms of headache, muscle aches, sore throat, and cough, or only mild ones, for at least 24 hours. As the P values indicate, the two zanamivir groups differed significantly from the placebo group but not from each other.

mivir was associated with a shorter — by three days — median time to the alleviation of symptoms than in the placebo group ($P=0.001$ for the comparison of placebo with inhaled zanamivir; $P<0.001$ for the comparison of placebo with intranasal and inhaled zanamivir). The cumulative fraction whose symptoms were alleviated increased steadily, so that approximately 90 percent had no symptoms or only mild ones through day 9 (Fig. 2). In comparison, symptoms were alleviated more slowly in the placebo recipients, and nearly 30 percent had not reached this end point by day 10. The patients who were treated earlier with zanamivir resumed their normal activities a median of one to two days before the respective placebo group (Table 3). In contrast, those treated more than 30 hours after the onset of symptoms had no significant reductions in these measures (Tables 2 and 3).

Cough was the most persistent individual symptom, lasting a median of four days among placebo recipients and three days among zanamivir recipients. Recipients of intranasal zanamivir tended to have shorter periods of nasal congestion (median, two days) than the other groups (three days). The

TABLE 2. TIMES TO THE ALLEVIATION OF MAJOR SYMPTOMS OF INFLUENZA.*

VARIABLE	PLACEBO			INHALED ZANAMIVIR			INHALED AND INTRANASAL ZANAMIVIR			COMPARISON OF INHALED ZANAMIVIR AND PLACEBO†		COMPARISON OF INHALED AND INTRANASAL ZANAMIVIR AND PLACEBO†	
	MEDIAN	MEAN ±SD	NO. OF SUBJECTS	MEDIAN	MEAN ±SD	NO. OF SUBJECTS	MEDIAN	MEAN ±SD	NO. OF SUBJECTS	DIFFERENCE (95% CI)	P VALUE	DIFFERENCE (95% CI)	P VALUE
	day			day			day						
All subjects (intention-to-treat analysis)	5	6.0±2.9	144	5	5.3±2.6	132	4	5.5±2.8	141	−0.7 (−1.4 to 0)	0.04	−0.6 (−1.2 to 0.1)	0.09
Confirmed influenza infection	5	6.3±2.9	89	4	5.4±2.7	85	4	5.3±2.8	88	−0.8 (−1.7 to 0)	0.05	−1.0 (−1.8 to −0.1)	0.02
Fever at enrollment (temperature, ≥37.8°C)	7	6.8±2.8	54	4	5.3±2.6	46	4	5.1±2.5	51	−1.4 (−2.5 to −0.4)	0.01	−1.8 (−2.8 to −0.8)	0.001
No fever at enrollment	4	5.5±3.0	35	4	5.5±2.9	39	4	5.7±3.0	37	0.1 (−1.3 to 1.4)	0.93	0.2 (−1.2 to 1.6)	0.73
Initiation of treatment													
≤30 hr after onset of symptoms	7	7.0±2.7	45	4	5.1±2.2	43	4	4.8±2.6	42	−1.9 (−2.9 to −0.8)	0.001	−2.2 (−3.2 to −1.1)	<0.001
>30 hr after onset of symptoms	4	5.5±3.0	44	5	5.8±3.1	42	5	5.8±2.8	46	0.3 (−1.0 to 1.5)	0.68	0.3 (−1.0 to 1.5)	0.70

*Alleviation of illness was defined as the absence of feverishness and the presence of no symptoms of headache, muscle aches, sore throat, and cough, or only mild ones, for at least 24 hours.

†P values were derived from the extended Mantel–Haenszel test. CI denotes confidence interval.

TABLE 3. TIMES TO THE RESUMPTION OF USUAL ACTIVITIES.

VARIABLE	PLACEBO			INHALED ZANAMIVIR			INHALED AND INTRANASAL ZANAMIVIR			COMPARISON OF INHALED ZANAMIVIR AND PLACEBO*		COMPARISON OF INHALED AND INTRANASAL ZANAMIVIR AND PLACEBO*	
	MEDIAN	MEAN ±SD	NO. OF SUBJECTS	MEDIAN	MEAN ±SD	NO. OF SUBJECTS	MEDIAN	MEAN ±SD	NO. OF SUBJECTS	DIFFERENCE (95% CI)	P VALUE	DIFFERENCE (95% CI)	P VALUE
		day			day			day					
Confirmed influenza infection	4	4.9±2.7	89	4	4.6±2.8	85	4	4.2±2.5	88	−0.3 (−1.1 to 0.4)	0.41	−0.8 (−1.5 to 0)	0.05
Fever at enrollment (temperature, ≥37.8°C)	5	5.1±2.6	54	4	4.5±2.8	46	4	4.4±2.4	51	−0.6 (−1.6 to 0.4)	0.23	−0.9 (−1.9 to 0.1)	0.06
No fever at enrollment	3	4.5±2.8	35	4	4.7±2.9	39	3	3.9±2.8	37	0.1 (−1.1 to 1.4)	0.81	−0.5 (−1.8 to 0.8)	0.44
Initiation of treatment													
≤30 hr after onset of symptoms	5	5.4±2.8	45	4	4.1±2.6	43	3	3.8±2.4	42	−1.3 (−2.3 to −0.2)	0.02	−1.7 (−2.7 to −0.6)	<0.01
>30 hr after onset of symptoms	4	4.4±2.5	44	5	5.1±2.9	42	4	4.6±2.7	46	0.7 (−0.5 to 1.8)	0.26	0.2 (−1.0 to 1.3)	0.80

*P values were derived from the extended Mantel–Haenszel test. CI denotes confidence interval.

duration of fever was relatively brief in all groups (median, two days), but this analysis was confounded by frequent use of antipyretic drugs.

The incidence of complications of influenza for which antibiotics were prescribed was 12 percent in the placebo group, 8 percent in the group given inhaled zanamivir, and 8 percent in the group given intranasal and inhaled zanamivir. Otitis media was diagnosed in 2 percent of influenza-infected patients, sinusitis in 3 percent, bronchitis in 2 percent, and pharyngitis and tonsillitis in 2 percent.

Virologic Measures

Among infected patients, the median duration of viral shedding tended to be shorter among those given inhaled zanamivir (four days) or intranasal and inhaled zanamivir (four days) than in those given placebo (six days). In the group given inhaled and intranasal zanamivir, the titers of virus recovered in nasal washings were lower by a mean of 2.1 $\log_{10}$ $TCID_{50}$ per milliliter on the second treatment day and by 1.5 $\log_{10}$ $TCID_{50}$ per milliliter on the fourth day as compared with placebo ($P=0.05$ for the comparison with placebo by analysis of the AUC). As expected, no reductions in nasal viral titers were noted in the group given inhaled zanamivir. None of the groups had increases in viral titers after the cessation of therapy.

Among the infected patients, the frequencies of increases in antibody titers of fourfold or greater on hemagglutination-inhibition testing did not differ among the placebo group (53 percent of patients), the group given inhaled zanamivir (64 percent), and

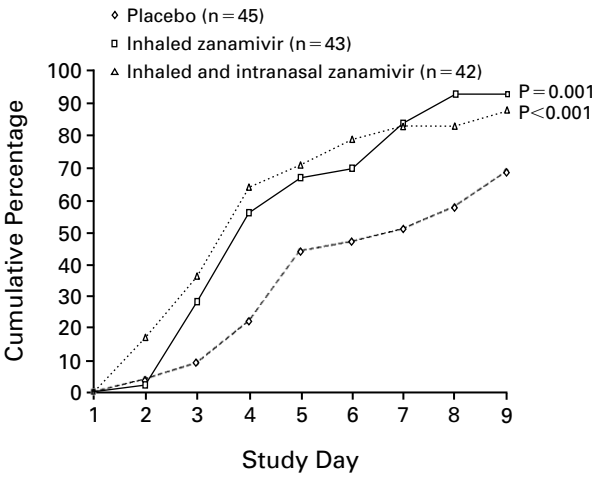

Figure 2. Alleviation of Symptoms in Patients Infected with Influenza A or B Virus Who Were Treated within 30 Hours after the Onset of Symptoms with Inhaled Zanamivir, Inhaled and Intranasal Zanamivir, or Placebo.

Alleviation of illness was defined as the absence of feverishness and the presence of no symptoms of headache, muscle aches, sore throat, and cough, or only mild ones, for at least 24 hours. As the P values indicate, the two zanamivir groups differed significantly from the placebo group but not from each other.

the group given intranasal and inhaled zanamivir (56 percent). Similarly, the mean ($\pm$SD $\log_2$) increase in titers in paired samples on hemagglutination-inhibition testing did not differ among the groups (2.2 ± 1.6, 2.4 ± 1.4, and 2.1 ± 1.8, respectively).

Tolerance

Six patients in each group withdrew during treatment. The numbers of patients who missed four or more doses because of noncompliance or withdrawal were also similar in the three groups (13 patients in the placebo group and 8 each in the group given inhaled zanamivir and intranasal and inhaled zanamivir).

Possible drug-related adverse events were reported by 18 percent of 144 patients assigned to placebo, 23 percent of 132 patients assigned to inhaled zanamivir, and 25 percent of 141 patients assigned to intranasal and inhaled zanamivir. During drug administration, adverse events related to the upper respiratory tract (9 percent of patients given placebo, 7 percent of those given inhaled zanamivir, and 11 percent of those given intranasal and inhaled zanamivir) or gastrointestinal tract (5 percent, 7 percent, and 9 percent, respectively) were the most common, but these reactions were difficult to distinguish from symptoms due to the underlying illness. The frequencies of local irritation of the nose (5 to 6 percent) or eyes (<1 percent) were similar in the three groups. No drug-related effects on blood counts, blood chemical values, or urinalysis results were found (data not shown).

DISCUSSION

The results of these studies show that administration of the novel neuraminidase inhibitor zanamivir directly to the respiratory tract is associated with significant clinical and antiviral effects in adults with naturally occurring influenzavirus infections. The magnitude of the observed clinical benefit was a one-day (approximately 20 percent) reduction in the time to the alleviation of major influenza symptoms. However, the degree of benefit was greater in those with more pronounced illness, as indicated by the presence of fever at enrollment, and in those treated within 30 hours after the onset of symptoms. In these groups the median times to the alleviation of influenza symptoms were approximately 40 percent less (shorter by three days) than that in the respective placebo group. These findings are consistent with the relatively rapid resolution of uncomplicated influenza in previously healthy adults and the need for early antiviral drug administration. The magnitude of the clinical benefit observed in this study appears to be at least as great as that in earlier trials of amantadine and rimantadine for acute febrile influenza A illness in adults.[17-20] In addition, as predicted by the results of in vitro studies,[8,9] tests in animal models,[8,10] and experimental studies in humans,[21] the antiviral spectrum and clinical effectiveness of zanamivir included influenza B virus infections.

As expected, zanamivir was of no benefit in persons without laboratory-documented influenzavirus infection. Although the clinical diagnosis of typical influenza in adults is highly predictive of virologically confirmed infection during brisk epidemics, in our study a relatively high proportion of enrolled patients did not have confirmed influenza. This observation indicates the limitations of this approach and the need for rapid viral diagnosis when the likelihood of infection is not high.

Topical zanamivir was generally well tolerated, and the frequency of local irritation was low. One source of concern was that the inhalation of dry powder would prove to be irritating in those with acute influenza, which can cause mucosal damage and airway hyperreactivity.[12] Although we did not measure pulmonary function, the more rapid resolution of cough in recipients of zanamivir than in placebo recipients is reassuring. Furthermore, previous studies of uninfected patients with asthma found no evidence of clinical intolerance or spirometric deterioration after multiple-dose inhalations of zanamivir for two weeks.[22] Because of the severity of influenza in patients with underlying disease of the airways (such as asthma, chronic bronchitis, emphysema, or cystic fibrosis) and the anticipated use of an antiinfluenza agent in these high-risk patients, it will be important to collect further safety data in such patients. The administration of zanamivir did not impair the humoral immune response to infection in our patients.

Intranasal zanamivir did not significantly enhance the clinical benefit observed with inhaled drug alone. However, this study was not designed to detect differences between the zanamivir groups, so it is premature to conclude that intranasal dosing was not beneficial. For several outcome measures, the group given both intranasal and inhaled zanamivir tended to benefit more than the patients given placebo, even though the former group had a higher proportion of smokers and smoking is a risk factor for more severe influenza.[23] Intranasal zanamivir also reduced viral titers in the upper respiratory tract. Although this was not tested directly in this study, such reductions might reduce the risk of transmission of influenzavirus. Sustained antiviral effects in the nasal passages would probably be required to reduce the likelihood of local complications such as otitis media and sinusitis. In this regard, the number of complications leading to the use of antibiotics tended to be lower in the zanamivir groups than in the placebo group, but our samples were too small to detect significant differences in these relatively infrequent events.

The patterns of drug deposition are not well characterized with the delivery devices used in these tri-

als. Previous studies have shown broader distribution within the nasal passages of materials administered by intranasal drops than by coarse sprays.[24,25] This difference in distribution is associated with less pronounced antiviral effects of aerosolized agents than of drops in experimental influenza[11] and rhinovirus[26] infections. Similarly, inhalations must be carefully administered to reach the lower airways and avoid being deposited on the oral mucosa or posterior pharynx. Our patients gave themselves the study drugs, which probably resulted in suboptimal delivery of zanamivir in some cases. Consequently, it remains uncertain whether the effects observed in our study represent the maximal benefits that might be derived from antiviral treatment of acute influenza with zanamivir. However, our findings indicate that topically applied zanamivir is an effective therapy for uncomplicated influenzavirus infections in adults, especially when initiated early. Pharmacologic inhibition of influenzavirus neuraminidase may prove to be a useful therapeutic strategy.

Drs. Hayden, Treanor, Aoki, and Nicholson have served as ad hoc consultants to Glaxo Wellcome.

APPENDIX

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