EARLY TREATMENT OF THE COMMON COLD WITH INTRANASAL INTERFERON ALPHA-2A (Ro 22-8181): A PRELIMINARY PILOT STUDY

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INTRODUCTION

It is well established that intranasal IFN Alpha-2a is effective in preventing experimental and natural rhinovirus-induced common cold (1-3). Seven-day contact prophylaxis is well tolerated and approximately 80% of rhinovirus respiratory virus infections are prevented (4, 5). There is little information about therapeutic effect of intranasal interferon in symptomatic patients. Hayden and Gwaltney (6) found only modest effects on nasal symptoms in experimentally induced rhinovirus infection when treatment was initiated 28 hours after the virus inoculation.

In this double-blind, placebo controlled study, we examined the tolerance and efficacy of early treatment of natural common colds with intranasal IFN Alpha-2a.

PATIENTS AND METHODS

Study Population

From November 15, 1985 to February 3, 1986, fifty adults, belonging to the staff of University Children's Hospital, Basel were admitted to the study. The patients were asked to enter the study when they felt that they were developing respiratory tract infection and had experienced at least one of the following symptoms: sore throat, runny nose, stuffy nose, cough or sneezing, for less than 24 hours. There were 36 females and 14 males.

A physical examination was performed at the pre-study visit. Blood was taken for haematologic tests (total white blood cell count (WBC) and differential and erythrocyte sedimentation rate (ESR)). Nasopharyngeal mucus was aspirated for rapid diagnosis and virus isolation. The patients received daily personal symptom cards (PSC) to record the signs and symptoms of the disease twice daily (morning and evening) for the following 5 days. The patients were advised to score their symptoms as follows: 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms. The participants were not allowed to use nasal decongestants or prostaglandin synthetase inhibitors (e.g. aspirin) during the observation period.

Re-examinations were performed 6 and 21 days after the first visit. On day 21 blood was taken for virus serology. Seven patients (4 from IFN Alpha-2a group and 3 from placebo group) were excluded from the efficacy analysis due to protocol violations (4 for incomplete or incorrect completion of PSC, 2 for having treatment assessment performed 3 days after treatment start and one for starting treatment 2 days after pre-trial assessment).

Medication and randomisation

By computer-generated code, the patients were randomly assigned to receive either recombinant IFN Alpha-2a or placebo. Patients were instructed to use the nasal spray 4 times daily (2 sprays into each nostril at approx. 6 hour intervals). Each spray contained 0.72 million IU of IFN Alpha-2a in 0.09 ml volume or an equivalent volume of placebo solution. The total daily dose of interferon was 12 million IU. The effect of medication was considered to be evaluable if the patient had used the drug for at least 4 of the 5 days prescribed. The compliance was checked by measuring the amount of liquid in the returned spray bottles.

Virologic studies

Nasopharyngeal secretion specimens (usually 0.5–2.0 ml) were collected by suction through the nostrils with a disposable mucus extractor (Vygon, Ecouen, France). The specimens were stored at -70°C . Rhinovirus isolation (cytopathic effect) was done on HeLa Ohio and MRC-5 cell lines. A double sandwich ELISA (7) was done from culture media to detect adenovirus, influenza A and B virus, parainfluenza virus type 1, 2, and 3 and respiratory syncytial virus antigens. In addition, the original mucus specimens were tested in parallel for these viruses by analogous enzyme immunoassays. Paired blood samples collected on days 1 and 21 were tested for viral antibodies using routine complement-fixation tests.

Antibody to IFN Alpha-2a

The paired serum samples taken at days 1 and 21 were tested by radio-immunoassay for the presence of specific antibodies to IFN Alpha-2a (8).

Statistics

Statistical analysis of total symptom scores was performed using an analysis of covariance with baseline score as covariate. Analysis of overall efficacy assessment (patients' judgement) and tolerability were carried out using Fisher's exact test (2-sided).

RESULTS

Forty-six patients entered the study within 24 hours after the onset of symptoms and signs of acute respiratory tract infection. Four patients entered within 48 hours. The major symptoms reported were stuffy nose (75%), sore throat (62%), and runny nose (36%). Fever was recorded in only one patient. The viral etiology of the acute respiratory tract infection could be confirmed in 37 of 50 patients (74%). Sixteen patients had rhinovirus infection, 8 parainfluenza virus type 1 or 2, 8 influenza A or B virus and 5 respiratory syncytial virus infection.

The overall efficacy assessment by the 43 evaluable patients on day 5 is shown in Table 1.

Forty-eight percent of the patients in interferon group and 8% in the placebo group found the trial medication to be "clearly" effective on day 5 of the study.

The median symptom score for all patients at baseline was 6.0 in both groups. The corresponding numbers at the end of the treatment were 1.0 in the interferon group and 3.0 in the placebo group. There was no significant difference between interferon and placebo in all patients or in patients with laboratory verified rhinovirus infection. The total score summed for all 10 timepoints (5 days) showed superior efficacy in the interferon group (median score 33.0, range 14–85) compared with the total

TABLE 1. Overall efficacy assessment of patients

Group	N	Efficacy Rating		
		Clearly No. (%)	Yes, a little No. (%)	None No. (%)
<hr/>				
<u>All patients</u>				
Interferon	21	10 (48)	4 (19)	7 (33)
Placebo	22	4 (18)	11 (50)	7 (32)
<u>Rhinovirus</u>				
Interferon	9	5 (56)	1 (11)	3 (33)
Placebo	4	0 (00)	2 (50)	2 (50)
<u>Non-rhinovirus</u>				
Interferon	12	5 (42)	3 (25)	4 (33)
Placebo	18	4 (22)	9 (50)	5 (28)

score in the placebo group (median score 52.0, range 13-175). However, when the sum of the scores over the 10 timepoints was adjusted for the baseline, this difference was not retained (7.2 in the placebo group and 6.9 in the interferon group) ($p \approx .45$). The imbalance in the size of the rhinovirus subgroups invalidated the comparison between the placebo and interferon groups. However, in the interferon group the rhinovirus subgroup ($n = 9$) showed a lower median symptom score (24.0) compared with the non-rhinovirus subgroup ($n = 12$) median symptom score (53.5).

Table 2 shows the number of patients with symptom score decreases by $\geq 50\%$ on days 3 and 5. At the end of the treatment 76% of the patients in the interferon group had a decrease in total symptom score by $\geq 50\%$ as against 52% in the placebo group. The difference was not statistically significant.

TABLE 2. Score reduction $\geq 50\%$ on days 3 and 5

Group	N	Day 3		Day 5	
		n	%	n	%
<hr/>					
<u>All patients</u>					
Interferon	21	9	(43)	16	(76)
Placebo	22	8	(36)	12	(55)
 <u>Rhinovirus</u>					
Interferon	9	6	(67)	7	(78)
Placebo	4	1	(25)	1	(25)
 <u>Non-rhinovirus</u>					
Interferon	12	3	(25)	9	(75)
Placebo	18	7	(39)	11	(61)

There were no differences in the numbers of patients reporting need for acetaminophen use, sleep disturbances or absences from work (data not shown). Bacterial type complications occurred in 3 patients in each treatment group (5 cases of bronchitis and one case of acute otitis media).

There were no withdrawals from the study due to treatment intolerance. Overall, one or more adverse effects were detected in 32% of placebo users and 52% of interferon users ($p = .252$). Intranasal adverse effects (Table 3) were the only clinically relevant adverse effects reported i.e. endonasal erosions, nosebleed or blood tinged mucus. None of the adverse effects were severe but 5/6 moderate adverse effects were in the active treatment group.

No patients developed antibodies.

TABLE 3. Adverse experiences during 5 day intranasal interferon or placebo treatment

	Interferon n = 25	Placebo n = 25
Blood-tinged nasal mucus	20%	20%
Nosebleed	12%	4%
Endonasal erosions	12%	4%
Nasal mucosal dryness	12%	12%
Total proportion of patients with one or more intranasal adverse effects	44%	32%

DISCUSSION

Hayden et al (5) and Douglas et al (4) have shown that daily post-contact prophylactic administration of 5 million IU once a day for 7 days prevents common cold in 39 and 41% of contacts compared with the placebo. The efficacies in preventing rhinovirus colds were 78% and 79% respectively. A recent study of Monto et al (9) reported prophylactic efficacy against rhinovirus colds to be 76%. They used 3 million IU daily dose given in two doses over a four week period. In these three studies no prophylactic efficacy was found against parainfluenza, respiratory syncytial or coronavirus infections.

In general short-term prophylactic intranasal interferon is well tolerated. Blood-tinged mucus, nosebleed or nasal mucosal erosions occur in 10-20% of the patients but only require premature discontinuation of therapy in rare cases when treatment is continued for more than one week. Thus rhinovirus infections can be effectively prevented with intranasal interferon but there is no efficacy against other respiratory viruses.

This study demonstrates that early treatment of common cold with 12 million IU daily intranasal IFN Alpha-2a has no clinically relevant effect on the severity of the signs and symptoms of the illness. However, 46% of the patients in the interferon group considered the treatment clearly ef-

fective compared to 19% in the placebo group. In the rhinovirus cold subgroup the corresponding numbers were 56% and 0%. It may be that the scoring system used in the study is not sensitive enough to detect the obvious modest therapeutic effect of intranasal interferon. Our findings, however, agree with those of Hayden and Gwaltney (6) who recorded only minimal effect of interferon treatment on the symptoms of established experimental rhinovirus infection.

This study was conducted during the late fall season when many different respiratory viruses exist in the community. We detected the viral etiology in 74% of cases. This exceptionally high number is probably due to the fact that samples were collected during the first 24-48 hours of the illness which is the optimal time. No transport media were used for virus isolation, because samples were collected in the laboratory. Furthermore, new sensitive techniques were used to detect viral antigens in the nasopharyngeal mucus and in the cell culture media. Although the study started in November, rhinoviruses were the most common viruses found (32%). In addition, parainfluenza virus type 1 and 2, influenza A and B and respiratory syncytial viruses were found. These infections could not be clinically differentiated from rhinovirus infections. Intranasal interferon has neither prophylactic nor therapeutic effect on these latter respiratory virus infections. Thus during the late fall season, specific virus diagnosis to exclude a non-rhinovirus etiology is desirable if interferon is to be used effectively for prophylaxis.

Forty-four percent of the patients in the interferon group and 32% of the patients in the placebo group had local nasal adverse effects (blood tinged mucus, nosebleed and/or nasal mucosal erosions). The figures are higher than earlier reported with lower doses and fewer daily administrations. In this trial, the four times daily drug administration which induces a considerable amount of mechanical irritation to the nasal mucosa was certainly a major etiological factor. This view is supported by the observation of Monto et al (9) who reported that once a day dosing has less side effects than twice a day dosing.

CONCLUSION

In conclusion, the observations of this study suggest that intranasal IFN Alpha-2a early treatment has no clinically relevant therapeutic effect on the severity of (a) respiratory virus infections and (b) laboratory confirmed rhinovirus infections. The slightly increased frequency of non-serious intranasal adverse effects in the interferon group may be improved by reducing the frequency of daily administration.

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