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Intranasal interferon (rIFN-αA, Ro 22-8181) for contact prophylaxis against common cold: a randomized, double-blind and placebo-controlled field study

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Summary

The prophylactic efficacy of low-dose intranasal recombinant leucocyte interferon alpha (rIFN-αA, Ro 22-8181) was investigated under field conditions in 147 families (n = 587 participants), randomized to receive placebo or rIFN-αA intranasally in daily doses of 1.5 or 0.3×10^6 IU. Treatment was started within 2 days after the appearance of an index case in the household and was continued for 5 days. Clinical data of the index case and of all members of the household were recorded for 10 days. In index cases and all ill contact persons nasal washes were collected for rhinovirus isolation and immunochemical detection of other respiratory viruses. The local tolerance of the intranasal rIFN-αA was excellent. Both doses of rIFN-αA failed to exert therapeutic effects on established common cold or to prevent the spread of common cold within families. Prophylactic treatment with 1.5×10^6 IU did however shorten the duration of the cold (median of 2 days vs. 4 in the placebo group, $P = 0.01$) and reduced the severity of any ensuing common cold (median total score of 10.5 vs. 30, $P < 0.001$). No correlation was found between viral etiology (55% rhinoviruses vs. 13% other respiratory viruses, n = 122 nasal washes) and prophylactic efficacy or clinical severity.

interferon; common cold; respiratory infection

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Introduction

Prospects for a common cold vaccine to be developed in a near future are bleak [2]. The control of common cold has therefore to rely on personal hygiene (e.g., implying the use of disposable, plain or virucidal nasal tissues [5,11]) or on the use of topically administered antiviral substances [2]. Prophylactic application of human leukocyte (Hu) or recombinant (r) interferon alpha (IFN-α_2), given intranasally, substantially reduces both the symptoms and virus shedding in volunteers experimentally infected with rhinovirus [13,14]. In placebo-controlled field studies 10×10^6 IU of HuIFN-α_2 [1,4] as well as low doses of $2.0–2.5 \times 10^6$ IU of IFN-α_2 [3,9,15] given daily for 3–4 weeks reduced the laboratory-documented rhinovirus infection rates. In neither study, however, could a clinical benefit be demonstrated from the use of the medication, as 20–50% of participants in the interferon groups complained about substantial nasal irritation after more than 10 days application [1,3,4,9,15]. Mucosal abnormalities [10] were demonstrable already at a daily dosage of $2.0–2.5 \times 10^6$ IU of IFN-α_2 [3,9]. The poor local tolerance renders long-term intranasal administration of IFN-α_2 a non-feasible strategy for prophylaxis of respiratory virus infection.

In the present placebo-controlled study we evaluated the efficacy of short-term interferon treatment of index cases combined with post-exposure prophylactic treatment of members of their household.

Patients and Methods

To be included in the study families had to consist of 3–6 persons with a minimal age of 3 years for the prophylactic treatment. The following definitions were used: index case = subject ill for $\leqslant 2$ days before start of treatment (proper index case) or contact person ill on day 1 of family treatment (parallel infection); contact person = no signs of common cold on days 1 and 2 of the family treatment; not evaluable for contact prophylaxis was a person if the cold started on day 2 of treatment or if the person was not treated. Symptoms and signs, graded on a 4-point severity scale, were recorded for all members of the household for 10 days on a self-assessment form. Two types of common cold were differentiated: a 'simple' cold (coryza only) and a flu-like cold (Table 1). The participants were not allowed to use nasal decongestants or prostaglandin synthetase inhibitors (e.g. aspirin) during the observation period.

The test substance was recombinant leukocyte interferon A (rIFN-αA, Ro 22-8181). All members of the family were instructed to apply the nasal spray twice daily (morning and evening) in each nostril for 5 days, starting within 2 days after the appearance of an index case in the household.

A nasal wash with warm saline was done in all index cases before treatment, if possible, or on day 1(–3) and in all ill contact persons within 2 days after appearance of symptoms. The nasal wash was transferred immediately into a transport medium and stored at –70°C. Rhinovirus isolation (cytopathic effect) was done on HeLa Ohio and MRC-5 cell lines; anti-interferon-αA was added in order to neutralize any rIFN-αA in the nasal wash specimens [7]. In addition a double sandwich ELISA was done with the

TABLE 1

Criteria for assessment of common cold severity[a]

Symptoms and signs[b]	
Coryza	Flu
Runny nose	Fever
Number of tissues used	Chill
Blocked nose	Fatigue
Sneezing	Hoarseness
Nose bleeding	Cough
Injected/tearing eyes	Expectoration
Headache ($\leq$1 point)	Chest pain
Sore throat ($\leq$1 point)	Confinement to bed
Ear-ache ($\leq$1 point)	Headache ($>$1 point)
	Sore throat ($>$1 point)
	Ear-ache ($>$1 point)

[a] Illness if total score $\geq$ 5 points; 'simple cold' if coryza score $\geq$ 4 and flu score $\leq$ 4 points; 'flu-like cold' if flu score $\geq$ 5 points with any coryza score.

[b] To be rated by the patient on a 4-point severity scale: 0 = none; 1 = slight; 2 = moderate; 3 = severe.

nasal wash specimens to detect adenovirus, influenza A/B, parainfluenza 1/2/3 and RSV antigen [6].

All participants were recruited from university hospital staff. After having given informed consent 191 families were randomized to receive placebo, 0.3 or 1.5×10^6 of rIFN-αA daily. They were provided with corresponding nasal sprays for each member of the household.

Results and Discussion

Of the 191 families enrolled, 147 experienced a new episode of common cold and started treatment with placebo ($n = 49$), 0.3×10^6 IU ($n = 47$) or 1.5×10^6 IU ($n = 51$) of rIFN-αA. Of the total of 587 active participants there were 189 index cases and 337 contacts; 61 cases were not evaluable. The age distribution (1–2 years, 3–12 years, 13–20 years, $>$20 years) of the three treatment groups was identical. The data from the pilot study done in the spring of 1983 [12] and from the trial carried out in the winter of 1983/84 were pooled for analysis.

The intranasal rIFN-αA treatment was well-tolerated. Prophylactic treatment of the 337 initially symptom-free contact persons did not influence the common cold infection rate (Table 2) but reduced the duration and severity of ensuing common colds (Fig. 1). Contact persons sharing bedrooms with index cases were not at a higher risk of contracting the cold. On the other hand, irrespective of the treatment, contact persons wearing glasses regularly had a slightly lower risk of contracting a cold than contact persons never wearing glasses [6/48 (12.5%) vs. 43/161 (26.7%), $P = 0.097$,

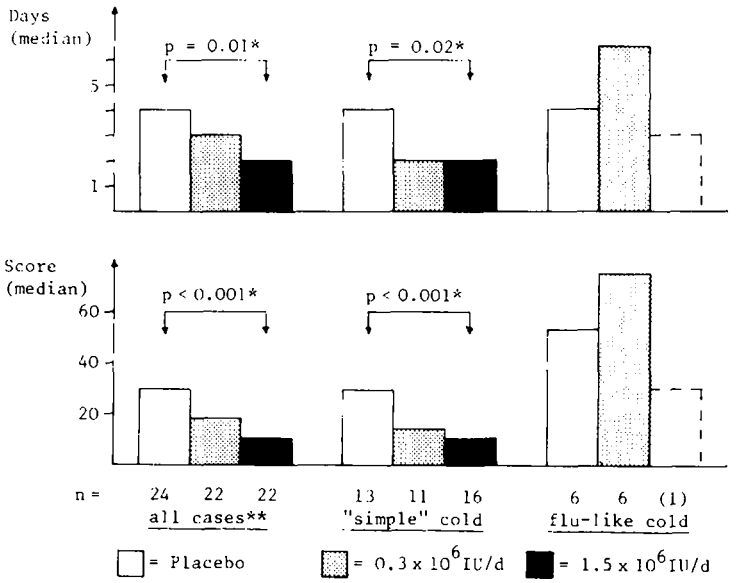

Fig. 1. Duration (days) and severity (total symptom score) of common cold among ill contact persons (n = 68) treated prophylactically with intranasal rIFN-αA. *Mann-Whitney U test. **Includes additional non-classifiable or intermediate cases.

TABLE 2

Development of common cold in initially symptom-free contact persons (n = 337) receiving prophylactic intranasal interferon treatment

Interferon dose (IU/day)	Number ill/total
Placebo	24/101
0.3×10^6	22/110
1.5×10^6	22/126[a]

[a] Fisher's exact test: not significantly different from placebo.

TABLE 3

Rhinovirus isolation and ELISA results for presence of other respiratory viruses in 122 nasal washes

Rhinovirus		67	(55%)
Adenovirus	1		
Influenza virus A/B	8/1		
Parainfluenza virus 1/2/3	4/1/1	16	(13%)
Respiratory syncytial virus	0		
No detectable virus or viral antigens		39	(32%)

Fisher's exact test]. In ill contacts presenting with a flu-like cold, interferon had no effect on the duration or severity of the illness. The 10-day observation period was too short to assess possible effects of interferon on the rate of complications (sinusitis, exacerbation of chronic bronchitis or precipitation of episodes of asthma) [1,5]. Simultaneous short-term treatment of the 189 index cases had no therapeutic effect (data not presented), as was also shown in a recent volunteer study [8].

The overall results of virus isolations are shown in Table 3. The majority of the 122 nasal washes were from index cases. Nasal washes were obtained from only half of the 68 ill contact persons. Among all the 8 ill placebo contacts with a virus identified in their families, no other than rhinoviruses were found compared to only 3 rhinoviruses out of 9 positive isolates in the 0.3×10^6 IU and 9 out of 14 in the 1.5×10^6 IU rIFN-αA groups. Knowing the high in vitro interferon-sensitivity of rhinoviruses, one would have expected less rhinovirus isolation among the ill contacts treated with interferon [1,4].

No correlation was found between viral etiology (rhinovirus or other respiratory viruses) and clinical type ('simple' or 'flu-like' cold) in the index cases or therapeutic efficacy in the ill contact persons.

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