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INTRANASAL INTERFERONS FOR CONTROL OF RESPIRATORY VIRAL INFECTIONS

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INTRODUCTION

Shortly after the discovery of interferon, its broad *in vitro* antiviral spectrum and potential ability to be applied directly to the upper respiratory tract were recognized as desirable characteristics for use in respiratory viral infections (1). In 1973 Merigan *et al* showed that intranasal administration of human leukocyte interferon (HuIFN-α [Le]) in a total dosage of 14 Mu over 4 days reduced seroconversion and illness rates following experimental rhinovirus type 4 challenge (2). A subsequent study at the MRC Common Cold Unit by Scott *et al* utilizing a lower dosage ($\geq$ 0.6 Mu) of fibroblast-derived interferon (IFN-β) found no evidence of protection (3). Scott *et al* later showed that high dosages of purified IFN-α(Le) (90 Mu over 4 days) protected against experimental rhinovirus type 9-induced illness (4). Studies conducted at Baylor College of Medicine identified rapid nasal clearance and insufficient contact time with the nasal mucosa, concentration dependency of antiviral action, and perhaps inactivation of IFN-β by nasal secretions as factors contributing to the relatively high interferon amounts needed to achieve antiviral effects in the nasal mucosa (5-9).

During the past five years the availability of highly purified, recombinant DNA-produced alpha (rIFN-α), and more recently beta (rIFN-βser) and gamma (rIFN-γ), interferons has stimulated considerable investigation. This review summarizes the results of recent clinical studies using intranasal interferons for the prevention and treatment of respiratory viral infections. It discusses the toxicity and virus-specific efficacy observed in studies of experimentally induced and naturally occurring infections.

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EFFICACY IN EXPERIMENTAL INFECTIONS

Rhinovirus

A number of randomized, double-blind, placebo-controlled studies have tested the prophylactic efficacy of intranasal interferons in experimental rhinovirus infection (reviewed in ref. 10). These trials have conclusively shown that two closely related species, recombinant interferon-alfa2b (rIFN-α2b) and leukocyte A interferon (rIFN-α2a) provide protection against experimental colds (11-17). Protection has been documented against five different rhinovirus serotypes, a finding which correlates with *in vitro* observations indicating that interferons have broad spectrum although variable activity against rhinoviruses (18).

Dose-related efficacy. The level of protection appears to depend on both the interferon dosage and the duration of administration prior to virus challenge. Scott *et al* found that a high rIFN-α2b dosage (22.5 Mu/day in 9 divided doses) begun 1 day prior to challenge was associated with protection against rhinovirus infection (51% efficacy) and against definite colds (100% efficacy) (11). Hayden *et al* found that an rIFN-α2b dosage of 46 Mu/day in 4 divided doses was 78% effective in preventing infection and 100% effective in preventing colds due to rhinovirus type 39 (12). Dose-response studies by Samo *et al* found that rIFN-α2a 10.0 Mu/day in 2 divided doses prevented illness (89% efficacy) and had discernible effects on rhinovirus type 13 shedding, but allowed subclinical infection to take place (13). A dosage of 2.4 Mu/day was also protective against illness (60% efficacy) but not infection, whereas a dosage of 0.7 Mu/day provided no protection against illness (14). Treanor *et al* found that even relatively low doses of rIFN-α2b (2.0 Mu/day) were protective against both infection (63% efficacy) and illness (84% efficacy) when begun one week prior to virus challenge (15). Turner *et al* also observed protection with rIFN-α2b 2.0 Mu/day begun 7 days prior to virus exposure (16). The mechanism by which interferon reduces symptoms without preventing infection is undefined, but this pattern of protection could have the advantage of preventing illness but not the development of immunity to the infecting virus.

Several studies have assessed the durability of interferon's *in vivo* effects. In studies employing biopsies of nasal mucosal epithelium from uninfected volunteers, Greenberg *et al* found in an *in vitro* assay that

significant antiviral effects lasted 18 hours but not 24 hours after *in vivo* interferon exposure (9). In contrast, Harmon *et al* found that human nasal epithelial cells exposed to HuIFN-α(Le) *in vitro* exhibited a prolonged (48-72 hours) antiviral state (8). In volunteer challenge studies, Hayden *et al* determined that a high rIFN-α2b dose (43 Mu) given once daily was associated with significant antiviral effects and provided protection (75% efficacy) against rhinovirus-induced illness (12). Phillpotts *et al* used varying dose regimens and intervals between interferon administration and virus challenge to conclude that administration 3 times per day provided optimal protection against experimental colds (17). However, as discussed below, field trials have established that dosing once daily is protective against natural rhinovirus colds. The available evidence suggests that prolonged protection against rhinovirus infection occurs after interaction of interferon with the respiratory mucosa.

Type of interferon. No study has directly compared the relative activities of different interferons. The effects seen with rIFN-α2b or rIFN-α2a appear similar and comparable to those observed with HuIFN-α(Le) (4,10). Using HuIFN-α(Ly) 8.1 Mu/day in 3 divided doses Phillpotts *et al* observed protection against illness (100% efficacy) but not infection (26% efficacy) after rhinovirus type 9 and 14 challenge (19). Higgins *et al* found that rIFN-βser (6.5 Mu/day in 3 divided doses) also provided protection against rhinovirus-induced illness (67% efficacy) but not infection (24% efficacy) (20).

Method of application. The method of applying interferon to the nasal mucosa appears to be an important factor in determining its intranasal distribution and antiviral effects. Using different methods to increase contact time with the nasal mucosa, Greenberg *et al* found that application of HuIFN-α(Le) by saturated cotton pledgets or by drops in volunteers pretreated with oral antihistamines, but not by drops alone, induced an antiviral effect in nasal epithelial cells (9). Relatively low doses of HuIFN-α(Le) (1-4 Mu), administered by saturated cotten pledgets or by aerosol to antihistamine-pretreated volunteers, were associated with modest reductions (40% efficacy) in illness frequency compared to placebo (21). When delivered by intranasal spray or drops, higher interferon dosages have been necessary to provide solid protection against

experimental rhinovirus colds.

Using solutions of radiolabelled human serum albumin, Aoki and Crawley (22) and more recently Hardy et al (23) found greater coverage of the nasal passages following administration by drops than by spray. In a study of rIFN-α2b treatment of experimental rhinovirus infection, Hayden et al indirectly compared these methods of administration and found that dosing by drops may have been associated with greater antiviral and clinical effects than by spray (24). Further studies are needed to determine the optimal methods for delivering interferons to the upper respiratory tract.

Therapeutic activity. Little information has been published on the possible therapeutic activity of intranasal interferon given after experimental rhinovirus infection. Hayden et al found that administration of rIFN-α2b (27.0 Mu/day in 3 divided doses for 5 days) beginning 28 hours after rhinovirus type 39 challenge was associated with significant decreases in the duration of viral shedding and titers of virus recovered in nasal washings, but only modest clinical benefit (24). In this study subjects treated with interferon by nasal drops experienced 40-50% reductions in peak nasal symptoms scores, mucus weights, and nasal tissue use compared to placebo recipients. A reduced duration of virus shedding could potentially confer a reduced risk of transmitting infection.

Coronavirus

At the MRC Common Cold Unit, Higgins et al found that a relatively high rIFN-α2a dosage (8.8 Mu/day in 3 divided doses for 4 days) provided protection against both infection (60% efficacy) and illness (85% efficacy) following coronavirus 229E challenge (25). The proportion of subjects excreting virus was significantly reduced on all post-challenge days in the interferon group. Turner et al used longer exposure to a lower dosage of rIFN-α2b (2.0 Mu/day for 7 days before and after coronavirus 229E challenge) and found significant but incomplete protection (44% efficacy) against coronavirus-induced illness (26). No reductions in infection rates or viral shedding were observed. These findings suggest that interferon efficacy is also dose-dependent in experimental coronavirus infection.

Influenza Virus

Studies involving different types of interferon and influenza viruses have found no significant protection against infection and variable protection against influenza virus-induced illness. Merigan et al found

that low dosages of HuIFN-α(Le) (0.8Mu/day) were not protective against influenza B virus challenge (2). Dolin et al found that intranasal administration of rIFN-α2b (10.0 Mu/day in 2 divided doses) starting two days before intranasal challenge with H1N1 subtype influenza A virus was associated with significant reductions in the number of days of virus shedding (36% fewer) and the frequency (66% efficacy) and severity of respiratory illness (27). Schiff used two lower dosages of rIFN-α2a (3.6 or 7.2 Mu/day) beginning on the same day as virus challenge with a H3N2 subtype influenza A virus and found no important effects on illness rates or the severity of illness (28). A trial by Phillpotts et al using HuIFN-α (Ly) 8.1 Mu/day found partial protection against illness (48% efficacy) following influenza A/H3N2 subtype challenge (19).

EFFICACY IN NATURAL INFECTIONS

The efficacy of intranasal rIFN-α2b in preventing naturally occurring respiratory viral infection and illness has been examined in randomized, double-blind, placebo-controlled field studies. As discussed below, there is considerable evidence that this interferon is effective for prophylaxis of natural rhinovirus infections. However, despite the broad antiviral spectrum of interferons in vitro and the protection observed in experimental coronavirus infections, no clear efficacy has been found against natural infection with viruses other than rhinovirus at the dosages tested (Table 1). For several viruses, insufficient information is

Table 1. Virus-Specific Prophylactic Efficacy of Intranasal rIFN-α2b

Respiratory Virus	Experimental Infection	Natural Infection
Rhinovirus	++	++
Coronavirus	++	0
Influenza A Virus	+	0
Parainfluenza Virus	N.D.	0
Respiratory Syncytial Virus	N.D.	N.D.
Adenovirus	N.D.	N.D.

ABBREVIATIONS: ++, definite protection; +, partial or variable protection; 0, no protection at dosages studied to date; N.D., not determined.

available to make determinations about specific efficacy. Possible explanations for the lack of broad prophylactic activity against all of the respiratory viruses include a lower susceptibility of these viruses to the in vivo antiviral effects of interferon compared to rhinovirus, and the inability to deliver interferon to sites, such as the lower respiratory tract, where infection may be initiated or continue during the course of natural infection. Whether higher dosages of intranasal interferon will provide protection against these other viruses remains to be determined.

Rhinovirus

Seasonal prophylaxis. In 1982 Farr et al conducted a 3-week prophylaxis study in Charlottesville, Virginia, during which adults self-administered nasal sprays of rIFN-α2b (10.0 Mu/day) or placebo once daily (29). Interferon was associated with complete protection (100% efficacy) against laboratory proven rhinovirus infection compared, to a 9% attack rate in the placebo group. In a similar study in Rochester, New York, Betts et al found that the same total interferon dosage given in 2 divided doses was also associated with protection (93% efficacy) against natural rhinovirus infections (30). However, these studies found discrepancies between virologic and clinical efficacy, and both were terminated one week earlier than planned because of the occurrence of nasal irritation in interferon recipients. Although interferon was associated with reductions in the occurrence of cough, the total number of episodes of respiratory illness which included nasal symptoms were significantly higher in interferon than placebo recipients due to the nasal side effects of the interferon.

Studies using lower interferon dosages have been conducted to identify clinically acceptable dose regimens for long-term use. Hayden et al found that rIFN-α2b (2.5 Mu/day in 2 divided doses) was associated with a high rate of minor nasal side effects (44% with blood in mucus) (31). This study was terminated after 12 days without evidence of protection, although it found no evidence of sensitization in those who had been previously exposed to the same interferon. During a 4-week study in Adelaide, Australia in 1983, Douglas et al found that rIFN-α2b (2.0 Mu/day in 2 divided doses) was associated with 87% protective efficacy against rhinovirus infection, compared to the 3.9% infection rate in the placebo group (32). However, 8% of interferon recipients withdrew because of nasal

side effects and 20% experienced blood-tinged mucus or bleeding for much or all of the study (32). No reductions in episodes or specific symptoms of respiratory illness were found. In 1983 Monto et al conducted two parallel 4-week studies at the University of Michigan (33). Among the 400 students assigned to rIFN-α2b 3.0 Mu/day in 2 divided doses or placebo, the protective efficacy against rhinovirus infection in the interferon group (3.5% infection rate) was 76% compared to placebo (14.6%). Among the 150 students given rIFN-α2b 2.5 Mu once daily or placebo, the efficacy against rhinovirus infection was 59% in the interferon group (6.7%) compared to placebo (16.2%). However, neither group of interferon recipients had reductions in numbers of respiratory illness episodes, although the severity of illness was significantly less in symptomatic interferon than placebo recipients. Both interferon groups had approximately 3-fold higher frequencies of blood-tinged nasal mucus during the study compared to placebo.

Although these studies have not directly determined dose-response in regard to efficacy, one study using a low dosage (1.7 Mu/day) found marginal protection against natural rhinovirus infection (34). The results of the different trials suggests that the minimally effective interferon dosage for prophylaxis of natural rhinovirus infections is approximately 2-3 Mu/day. However, long-term administration of rIFN-α2b at this dose level is not feasible for prophylaxis of rhinoviral infections in healthy adults because of the high incidence of nasal adverse effects.

Studies in high risk populations, such as those with asthma or chronic obstructive pulmonary disease, have found patterns of local nasal toxicity similar to those observed in healthy adults, but no evidence of lower respiratory tract intolerance determined clinically and by spirometric measurements (35). One 4-week study in asthmatic children and adults by Michael et al found no significant overall clinical benefit or protection against rhinovirus colds at a rIFN-α2b dosage of 2.0 Mu/day (36). A study in asthmatic children at the same dosage given over three 4-week periods showed no differences in the frequency of colds or asthma symptoms between interferon and placebo recipients (37).

Postexposure prophylaxis. Investigators at several institutions have completed studies to determine the usefulness of short-term intranasal rIFN-α for preventing illness in household contacts exposed to family

members with respiratory illness. In a study involving 147 families in Basel, Switzerland, Herzog et al administered low dosages of rIFN-α2a (0.3 or 1.5 Mu/day in 2 divided doses for 5 days) to both the index case and the contacts (38). Interferon did not prevent transmission of colds to family contacts, in whom secondary attack rates were 24% (placebo), 20% (IFN 0.3 Mu/day), and 17% (IFN 1.5 Mu/day), but its use appeared to reduce the severity and duration of illnesses that occurred in the contacts (38). In an 8-month study involving 60 familes in Charlottesville, Virginia, Hayden et al found that higher doses of rIFN-α2b (5.0 Mu once daily for 7 days) reduced the occurrence of total respiratory illness (14% secondary attack rate) in healthy family contacts by 39% compared to placebo (23%) (39). The protective effect appeared limited to rhinovirus infections, which were reduced by 88% in interferon recipients during spray use. In family members on interferon who were contacts of an index case with a laboratory documented rhinovirus cold, the risk of developing a respiratory illness or a proven rhinovirus cold was reduced by 79% compared to the placebo group. Minor mucosal bleeding occurred more often in interferon recipients (13.6% of spray uses) than placebo (7.7%), but no evidence of cumulative toxicity was observed (39).

Two subsequent studies utilizing a similar design have been conducted at other centers. Douglas et al found comparable results to the Charlottesville trial in 97 families studied over 6 months in Adelaide, Australia (40). This trial found a 41% reduction in episodes of definite respiratory illness and a 33% reduction in secondary days of nasal symptoms in interferon recipients compared to placebo. The protective efficacy against proven or suspected rhinovirus related illness was 62% overall and 78% in instances when rhinovirus was recovered from the index case. In a study involving 53 families in Seattle, Foy et al found a trend toward fewer illnesses (52% efficacy) during interferon (15% secondary attack rate) compared to placebo (32%) spray use, when rhinovirus was isolated from the index case or other family member (41).

These trials established that it is possible to interrupt the transmission of rhinovirus colds in the family setting by post-contact prophylaxis. This is the first strategy for using intranasal interferon to clearly show prevention of respiratory illness under natural conditions, primarily because rIFN-α2b is generally well-tolerated when used in this

manner. The efficacy and safety of postexposure prophylaxis needs to be studied in groups at increased risk for the complications of rhinovirus infection.

Therapeutic activity. Herzog et al reported that low dosages of rIFN-α 2a (0.3 or 1.5 Mu/day) had no therapeutic effect in natural colds (42). In a field trial involving adults with colds of diverse viral etiologies, Just et al recently found that rIFN-α2a (12.0 Mu/day in 4 divided doses for 5 days) provided no symptom benefit compared to placebo (43). A placebo-contolled study of rIFN-α2b treatment (10.0 or 20.0 Mu/day in four divided doses for 5 days) of natural rhinovirus colds has been recently completed at the University of Virginia (44). Preliminary analysis indicates that interferon treatment did not provide clinical benefit. These negative findings could relate to inability to initiate treatment early after the onset of symptoms, difficulty in effectively delivering interferon to the nasal mucosa in symptomatic individuals, or to the possibility that ongoing viral replication is not central to the pathogenesis of symptoms in rhinovirus infections.

Coronavirus

Very limited information is available about efficacy against natural coronavirus infections. Douglas et al found no evidence of protection against coronavirus infection in their seasonal prophylaxis study during which approximately 2% of interferon or placebo recipients had serologic evidence of coronavirus infection (32). This group also found no reduction in coronavirus infection in interferon recipients during the family-based prophylaxis study described above (40).

Parainfluenza Virus

During seasonal prophylaxis studies utilizing relatively low dosages of rIFN-α2b (2.0-3.0 Mu/day), no protection has been found against parainfluenza virus infection (31-33). Depending on the dose schedule, Monto et al found similar infection rates in those given interferon once (5.3% of subjects) or twice (7.1%) daily and in the corresponding placebo group (6.8% or 6.0%) (33). In those with parainfluenza virus-related infection, the severity but not the duration of illness appeared to be less in interferon recipients compared to placebo. In a family-based contact prophylaxis study, Hayden et al also found no evidence of protection against parainfluenza virus infection or illness, although the number of

infections for analysis was small (39).

Influenza Virus

One field trial conducted by Isomura et al found that small doses of HuIFN-α(Le) (0.01 Mu/day for 8 weeks) did not effect the frequency of serologically documented influenza or febrile episodes in young children, compared to placebo, but appeared to shorten the duration of episodes of fever and respiratory illness (45). A subsequent 3-month study by Saito et al used 0.05 Mu/day in adults and found no reduction in influenza A virus-related illness (38% attack rate in each group) (45). In a recent 4-week prophylaxis study in Newcastle, Australia, Tannock used rIFN-α2a dosages ranging from 1.5 to 6.0 Mu/day but did not observe protection against influenza A virus infection or illness (47). No evidence of protection against influenza virus transmission was observed in the family-based contact prophylaxis studies (39-41).

TOXICITY OF INTRANASAL INTERFERONS

Systemic Tolerance

In contrast to parenterally administered interferons, the only documented systemic toxicity of intranasal interferon has been transient leukopenia (Table 2). Reversible decreases in granulocyte counts have observed in some (12,24,29) but not all studies (4,11,30) utilizing higher interferon dosages. During a 3-week prophylaxis study, Farr et al observed leukopenia (WBC <4,000/mm^3) in 11% of those given rIFN-α2b 10 Mu/day (29).

Table 2. Adverse Effects Related to Intranasal Interferon

Toxicity	Symptoms	Signs
Systemic	None	Leukopenia
		Anti-IFN antibody
Nasal	Dryness, stuffiness	Mucosal friability
	Blood in mucus	Punctate bleeding
	Epistaxis	Erosions, ulcerations
		Histopathologic changes

Nearly two-thirds of the leukopenia patients had symptoms and signs of nasal irritation. In rhinovirus-challenged volunteers, Hayden et al found that 21% given rIFN-α2b 44 Mu/day developed mild leukopenia (12). The cause

of the changes in leukocyte counts has not been determined, but high interferon dosage and associated nasal mucosal irritation appear to be risk factors for its occurrence.

Another concern is the immunogenicity of synthetic interferons after repetitive or prolonged exposure. Two of over 1,300 individuals given intranasal interferon have been reported to develop transient circulating antibody against rIFN-α2b without recognized consequences (48). Limited attempts have failed to detect antibody in nasal secretions after exposure (49).

Local Tolerance

Although intranasal application avoids most of the systemic toxicities observed with parenteral administration, nasal mucosal toxicity has been a significant clinical problem (Table 2). The occurrence of nasal symptoms and mucosal abnormalities depends on both the dosage and duration of exposure. High dosages of HuIFN-α(Le) and HuIFN-α2b have been associated with a discernible increase in nasal symptoms after four days in some healthy subjects (4,11). As discussed above, relatively low doses of rIFN-α2b (2-3 Mu/day) are associated with significant increases in nasal complaints relative to placebo within 2 weeks of initiating administration (31-33). Similar types of dose-dependent nasal irritation have been observed within several weeks of initiating treatment with intranasal rIFN-α2a (12,13) or purified HuIFN-α(Le) (50). Indirect evidence suggests that local intolerance occurs sooner and perhaps more frequently when the same dosage is given in divided doses rather than once daily (29,30,33).

Placebo-controlled tolerance studies have found that intranasal rIFN-αs are associated with reversible histopathologic changes in nasal biopsy specimens (49, 51). In one study by Hayden et al healthy adults were given rIFN-α2b 8.5 Mu or placebo once daily for 28 days (49). Fifty-eight per cent of interferon recipients but none of those in the placebo group developed moderate or severe degrees of subepithelial chronic inflammatory cell infiltration. A subsequent study of rIFN-α2a (9.0 Mu/day for 4 or 10 days) used immunohistochemical techniques to determine the nature of the inflammatory infiltrate (51). This study found that 56% of interferon recipients developed increased numbers of subepithelial lymphocytes by the fourth day of exposure, prior to any symptoms of nasal irritation, and 60% by the tenth day. T-helper cells

were the principal type of lymphocytes observed in both the normal and the interferon-exposed nose. The histologic changes observed in the nasal mucosa appear to antedate the clinical intolerance observed and to be secondary to the immunologic activity of rIFN-α.

It is unclear whether it will be possible to identify an effective interferon regimen that is also well-tolerated during chronic administration. Other interferons that may offer the possibility of better therapeutic ratios include rIFN-βser (20, 52), IFN-αcon1, or possibly combinations of rIFN-α and rIFN-γ (53). In a recent tolerance study, Hayden et al found that rIFN-βser 3.0 or 12.0 Mu/day for 25 days was associated with less pronounced effects on nasal histopathology and better clinical tolerance, compared historically to studies of rIFN-α (52). Interventions which could modify the inflammatory but not the antiviral effects of intranasal interferon might improve the therapeutic ratios of available interferons.

SUMMARY

Studies have established that intranasal interferon is effective in preventing both experimental and naturally occurring rhinovirus infections. The results of studies with the current formulations of recombinant α-interferons do not suggest that long-term or seasonal prophylaxis is a feasible strategy for preventing respiratory viral infections in healthy adults. Postexposure prophylaxis with intranasal rIFN-α2b is clinically useful in preventing transmission of rhinovirus colds in the family setting. Treatment studies in natural colds have yielded discouraging results. Trials are needed to define the mechanisms of local toxicity and to assess alternate dose schedules, modes of delivery, and other interferon preparations.

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