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# Recombinant alpha-2 interferon gel treatment of recurrent herpes genitalis

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## Summary

Topical recombinant alpha-2 interferon treatment of recurrent genital herpes was studied in a randomized, double-blind, placebo controlled clinical trial. Three hundred and eighty-seven patients were treated at eight study centers with either interferon gel or placebo four times daily for four days. Interferon therapy caused a 26% decrease in the duration of viral shedding. For male patients, there were also significant decreases in the time to crusting (17%) and duration of pain (34%) and itching (21%). For patients with recurrent genital herpes, treatment with topical interferon was found to be effective in decreasing the duration of viral shedding and, for males, pain, itching and time to crusting.

Interferon; Topical; Herpes genitalis

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## Introduction

Interferons are a group of proteins produced by leukocytes and which have both antiviral and antiproliferative effects. Several human subspecies have been isolated and cloned using recombinant DNA technology with bacteria or yeast. Interferons have been demonstrated to inhibit the proliferation of herpes simplex viruses in vitro. Recurrent genital herpes is manifest by local lesions following reactivation of latent virus in nerve ganglia. Virus can be cultured from most lesions the first several days of an outbreak. Systemic interferon alpha administration causes significant toxicity, primarily a flu-like syndrome. Since the virus is present in cutaneous lesions, it was felt that topical treatment might give high enough local concentrations to inhibit viral replication yet be absorbed only minimally, avoiding systemic adverse effects. To test that hypothesis, we conducted a randomized, double-blind, placebo-controlled study of topical recombinant interferon alpha for treatment of recurrent genital herpes.

## Methods

### *Patients*

Three hundred and eighty-seven patients with a prior history of culture-positive genital herpes were included in the study. All patients gave written informed consent. Patients from eight study sites were enrolled. Because of excessive protocol violations, one study site was dropped early in the course of the study, and patients from that site were not included in this analysis. A summary of patient demographic data is given in Table 1. There were no clinically significant differences between the interferon and placebo groups.

### *Medication*

Recombinant interferon alpha-2 (Alferon® Gel, Interferon Sciences, New Brunswick, NJ) was supplied in 1-g tubes at a concentration of $6 \times 10^6$ IU/g. Each tube contained a sufficient amount of medication for one day's use in four divided doses. Placebo consisted of the same topical vehicle used for interferon and was identically packaged.

### *Protocol*

Patients were stratified by study site and randomized 60%/40% to either interferon or placebo. Most patients were screened and randomized into the trial prior to the treated episode of *H. genitalis*. An initial tube of interferon was dispensed at the time of study enrollment and was kept frozen until use. The patient was instructed to apply study medication to the affected area four

TABLE 1
Patient characteristics

| Characteristic | Treatment group | |
|---|---|---|
| | Interferon ($n$ = 237) | Placebo ($n$ = 150) |
| Sex | | |
| Male | 125 | 83 |
| Female | 112 | 67 |
| Marital status | | |
| Single | 182 | 117 |
| Married | 26 | 19 |
| Divorced | 19 | 8 |
| Other | 10 | 6 |
| Sexual preference | | |
| Heterosexual | 220 | 143 |
| Homosexual | 14 | 5 |
| Other | 3 | 2 |
| Age (years) | | |
| Median | 30.5 | 30 |
| Range | 17–67 | 17–50 |
| Number of episodes during past year | | |
| Median | 6 | 5 |
| Range | 0–50 | 0–30 |
| Time since last episode (days) | | |
| Median | 18 | 22 |
| Range | 0–365 | 0–551 |
| Herpes virus type | | |
| 1 | 3 | 1 |
| 2 | 180 | 123 |
| Not done/unknown | 54 | 26 |

times daily, starting within 12 h of the time a lesion was either observed or palpated and continuing for a total of 96 h. At the first clinic visit, which was to take place within 24 h of the onset of an outbreak, the patient was given an additional three tubes of medication.

Patients with known positive cultures who were not preenrolled in the study could be entered if they came into the clinic within 12 h of the onset of an episode. Patients so enrolled were given all of their medication at the time of enrollment. A total of 82 patients (48 in the interferon group and 34 in the placebo group) were entered into the trial by this method.

During the treatment period, patients were observed and the lesions cultured daily for five consecutive days and then on alternate days until all lesions were healed. Lesions that were present at the onset of treatment were cultured as one group; each lesion was swabbed once with a dacron-tipped applicator from the oldest to the most recent. The culture transport media contained anti-interferon

antibodies at a concentration found to be effective in neutralizing and preventing a drug carry-over effect of residual interferon (J. Douglas, unpublished data).

*Statistical analysis*

Comparisons between treatment groups, including quantitative demographic variables, such as age and duration of disease, were made using the Wilcoxon two-sample test. Qualitative variables, such as sex and marital status, were determined using chi-square contingency table analysis. For each efficacy variable, treatment group comparisons were based on the use of a proportional hazards model (Lee, 1980). The influences on treatment group comparisons attributed to the covariates of study center and number of lesions were estimated from the proportional hazards model. Additional quantitative efficacy measurements such as the number of recurrences at the time of the 3-month follow-up visit were analyzed using the Wilcoxon two-sample test. All statistically significant comparisons were determined by a two-sided $P$ value of $\leqslant 0.05$.

Safety data were analyzed by comparing the proportion of patients in each treatment group who experienced one or more adverse reactions. Statistical comparisons were determined by using a chi-square contingency table analysis; statistical significance was determined if $P \leqslant 0.05$.

Some patients did not comply with the protocol, usually because of a violation of the treatment schedule. Analyses were based on the 'intent to treat' approach so that all patients enrolled at seven centers were included in the evaluations of both safety and efficacy.

## Results

*Side effects*

Table 2 gives the number of patients reporting various side effects during the study as well as the number of occurrences. Thirteen percent of interferon-treated and 12% of placebo-treated patients reported side effects. These included local pain, tingling, burning, pruritus, and, rarely, other local and systemic effects. There were no significant differences between the treatment groups with respect to any adverse effects, except for local pain, in which the incidence was 4% for interferon-treated versus 9% for placebo-treated patients, and for all systemic effects 3% for the interferon group versus none for patients receiving placebo (both comparisons $P \leqslant 0.05$). Statistical significance for systemic effects was achieved only by including nausea, fatigue, fever, headache and muscle aches together.

TABLE 2
Side effects

| | Interferon | | Placebo | |
|---|---|---|---|---|
| | Patients (%) ($n$ = 237) | Occurrences | Patients (%) ($n$ = 150) | Occurrences |
| No adverse effects | 207 (87) | | 132 (88) | |
| Adverse effects | 30 (13) | 47 | 18 (12) | 26 |
| Local pain | 9 (4) | 18 | 14 (9) | 18 |
| Tingling | 4 (2) | 4 | 3 (2) | 3 |
| Burning | 6 (3) | 7 | 4 (3) | 4 |
| Local pruritus | 2 (1) | 2 | 0 | 0 |
| Other, local | 4[a] (2) | 4 | 1[b] (1) | 1 |
| Systemic | 8[c] (3) | 12 | 0 | 0 |

[a]Vaginal numbness (1), penile swelling (1), foreskin swelling (1), wetness (1).
[b]Pressure.
[c]Nausea (3), fatigue (2), fever (2), headache (2), muscle ache (1), unspecified (1).

## *Efficacy*

The duration of various parameters was defined as the time from initial application of study medication to the time that the parameter became persistently negative. The duration of viral shedding is shown in Table 3. Seventy-eight percent of both interferon- and placebo-treated patients had initial lesions that were culture positive. The mean duration of viral shedding was 4.0 days for interferon-treated patients and 5.4 for patients receiving placebo (hazard ratio = 0.74, $P = 0.0001$). This is shown graphically in Fig. 1. The differences in viral shedding were greater for women than for men.

TABLE 3
Objective efficacy measures

| | Interferon | | Placebo | | Relative | |
|---|---|---|---|---|---|---|
| | $n$ | Mean ± SE | $n$ | Mean ± SE | Risk index | $P$ |
| *Duration of viral shedding (days)* | | | | | | |
| All patients | 184 | 4.0 ± 0.2 | 117 | 5.4 ± 0.4 | 0.74 | 0.0001 |
| Males | 102 | 4.4 ± 0.3 | 64 | 5.3 ± 0.5 | 0.82 | 0.039 |
| Females | 82 | 3.3 ± 0.2 | 53 | 5.4 ± 0.6 | 0.64 | 0.0001 |
| *Time to crusting (days)* | | | | | | |
| All patients | 237 | 4.5 ± 0.2 | 150 | 4.8 ± 0.3 | 0.91 | 0.084 |
| Males | 125 | 4.4 ± 0.3 | 83 | 5.0 ± 0.4 | 0.83 | 0.017 |
| Females | 112 | 4.7 ± 0.2 | 67 | 4.6 ± 0.3 | 1.0 | 0.95 |
| *Time to reepithelialization (days)* | | | | | | |
| All patients | 237 | 6.6 ± 0.2 | 150 | 6.5 ± 0.3 | 0.96 | 0.32 |
| Males | 125 | 7.2 ± 0.3 | 83 | 7.0 ± 0.4 | 0.94 | 0.23 |
| Females | 112 | 6.0 ± 0.2 | 67 | 5.8 ± 0.4 | 0.98 | 0.78 |

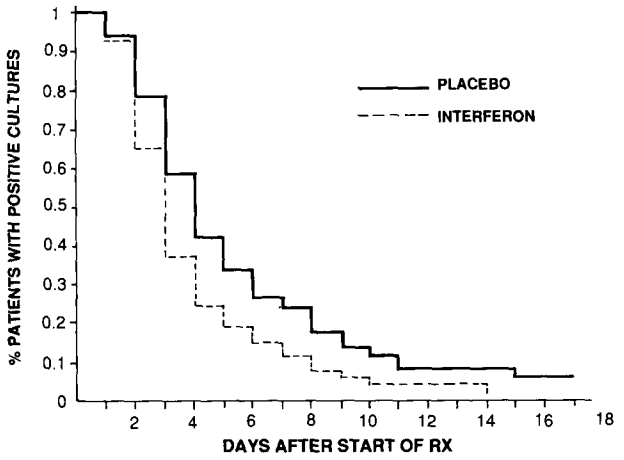


Fig. 1. Duration of viral shedding.

Interferon caused an 18% decrease in duration of viral shedding for men, but a 36% decrease for women.

A significant difference in time to crusting was seen for men, 4.4 vs. 5.0 days, $P=0.017$. No significant difference was seen for women. As can be seen in Table 3, interferon treatment had no effect on reepithelialization, 6.6 days for the interferon group vs. 6.5 days for patients receiving placebo.

Table 4 shows that males treated with interferon experienced more rapid relief of pain than those receiving placebo, with mean durations of 3.4 and 4.9 days, respectively ($P=0.005$). This was not true for females, however. Males treated with interferon experienced more rapid relief of itching than those receiving placebo. The mean duration of itching was 3.9 days for those treated with interferon, versus 4.5 days for those receiving placebo ($P=0.038$). No significant difference in duration of itching was seen for female patients.

TABLE 4

Subjective efficacy measures

| | Interferon | | Placebo | | Relative | |
|---|---|---|---|---|---|---|
| | *n* | Mean ± SE | *n* | Mean ± SE | Risk index | *P* |
| *Duration of pain (days)* | | | | | | |
| All patients | 147 | 3.9 ± 0.2 | 85 | 4.2 ± 0.4 | 0.92 | 0.32 |
| Males | 64 | 3.4 ± 0.3 | 36 | 4.9 ± 0.9 | 0.66 | 0.005 |
| Females | 83 | 4.3 ± 0.3 | 49 | 3.8 ± 0.5 | 1.09 | 0.43 |
| *Duration of itching (days)* | | | | | | |
| All patients | 166 | 3.9 ± 0.2 | 103 | 4.1 ± 0.4 | 0.97 | 0.67 |
| Males | 90 | 3.9 ± 0.3 | 52 | 4.5 ± 0.7 | 0.79 | 0.038 |
| Females | 76 | 3.9 ± 0.3 | 51 | 3.4 ± 0.3 | 1.12 | 0.40 |

No effect was seen on recurrences reported at the 3-month follow-up visit. For the 216 interferon- and 135 placebo-treated patients, for whom follow-up data were available, the median number of recurrences over three months was 1.0 in both groups, and the mean time to next episode was 5 weeks.

## Discussion

Herpes genitalis is one of the most common sexually transmitted diseases, its incidence having risen significantly over the past several decades (Corey, 1984). The most effective therapy to date has been acyclovir. In recurrent disease, topical acyclovir was found to decrease viral shedding in men only, with a trend toward decreased duration of pain in men (Corey et al., 1982). Given at the onset of an episode, oral acyclovir decreases the duration of viral shedding and hastens reepithelialization, but shows only a trend toward decreasing the duration of pain (Reichman et al., 1984). For good control, it must be taken prophylactically several times daily (Mertz et al., 1988; Mattison et al., 1988). As no current therapy can eradicate the virus in the nerve ganglia, the present goal of treatment is to suppress or shorten episodes and relieve symptoms.

Interferons have been shown to inhibit herpes simplex virus proliferation in vitro (Overall et al., 1980). Although an early clinical trial reported promising results with topical human leukocyte interferon (Ikic et al., 1973), several recent controlled trials have yielded conflicting results. In two placebo-controlled studies with parenteral alpha interferon, no benefit was seen but toxicity was significant (Gnann et al., 1984; Eron et al., 1986). Another study did show enhancement of reepithelialization with interferon treatment (Lassus et al., 1984). In an additional study in which patients with primary herpes were treated for 12 weeks, a decrease in the duration and severity of recurrences was seen following the initial episode (Mendelson et al., 1986).

Two recent studies using topical alpha interferon failed to demonstrate significant benefit (Friedman-Kien et al., 1986; Eron et al., 1987). The former study showed a significant delay in reepithelialization with high concentration topical interferon. The delay in reepithelialization is not surprising, considering the fact that inhibition of cell proliferation is a major effect of interferon treatment.

Our preliminary work (Interferon Sciences, Inc., unpublished data) with natural alpha interferon indicated that early treatment of episodes may shorten viral shedding. In some situations, however, reepithelialization was impaired with interferon treatment. In designing the therapeutic regimen used for this study, we decided to start treatment at a time when absorption of interferon should be high, that is once a lesion has begun to form. We used a high concentration of interferon and treated long enough to cover the natural period of viral shedding. We shortened the duration of therapy from that used in the preliminary studies to decrease the likelihood of delaying reepithelialization.

Although viral shedding was significantly shortened in both males and

females, symptomatic improvement was seen in men only. The reason for this difference is unclear, but may have been due to differences in the integument in males versus females. It is interesting to note that 48% of all males and 74% of females in the study noted pain during the episode of herpes treated; the incidence of culture positivity was 80% and 75%, and of itching 68% and 71%, for males and females, respectively.

In studies with systemic interferon treatment of genital herpes, most patients have experienced significant toxicity (Kuhls, 1986). This is in contrast to the results of treatment with topical interferon, where systemic toxicity was almost never seen and local toxicity was minimal. It is interesting to note that the incidence of local pain on application of medication was significantly lower in patients treated with interferon than in those receiving placebo.

For patients with very frequent outbreaks, suppressive therapy with acyclovir may be appropriate. For those with an episode not more frequently than every two to three months, taking acyclovir several times daily for many months may be less desirable. For these patients, a topical treatment could be useful. In this study, topical alpha interferon significantly shortened the duration of viral shedding in both men and women. In men, both the duration of pain and itching were significantly decreased with the use of topical interferon.

Topical recombinant alpha-2 interferon, with its lack of toxicity and significant effects on viral shedding and symptomatology, may have future use in the management of recurrent genital herpes. Further work remains to be done in optimizing vehicles, concentrations, and application schedules or examining combinations with other agents.

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