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Therapy of Genital Herpes with Topically Applied Interferon

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Ninety-four patients with recurrences of genital herpes were randomized in a double-blind trial to receive topical therapy for 5 days with either alpha-2a interferon at 30 × 10^6 IU/ml or 10 × 10^6 IU/ml or placebo six times daily. No differences were noted between either interferon dose and placebo with respect to the duration of viral shedding, the time to crusting, or the time to healing of herpetic lesions. Aqueous solutions of alpha-2a interferon applied topically to unroofed vesicles do not appear to be clinically useful in the treatment of recurrences of genital herpes.

Genital herpes infections may recur an average of four times per year in 80 to 90% of patients experiencing a first episode (2). Oral acyclovir may decrease the duration of an individual outbreak (12) or significantly suppress the frequency and severity of outbreaks when used on a daily basis (5, 15). No effect on subsequent recurrences has been noted, however, once therapy with acyclovir is discontinued. Interferon has been shown to possess activity against both herpes simplex virus types 1 and 2 in vitro (1, 11) and in animal experimental models (17). One study using intramuscular administration of recombinant alpha-2b interferon suggested some clinical efficacy in the therapy of genital herpes, but its parenteral administration was accompanied by significant toxicity (10). Other studies on the prevention (6) or treatment (7) of recurrent episodes of genital herpes have not demonstrated significant clinical benefits of parenteral administration of recombinant alpha-2b interferon. Nevertheless, the findings that endogenous interferon levels within herpes labialis vesicles increase with time (13) and that topical interferon alone and in combination with acyclovir or trifluorothymidine was clinically effective in the treatment of ocular herpes simplex infections (3, 4, 8, 16) suggested that topical interferon therapy of genital herpes attacks might be a reasonable idea. In an attempt to increase the convenience of administration of interferon and to reduce the toxicity of parenteral administration while potentially increasing clinical efficacy, we conducted a double-blind, placebo-controlled trial of topically applied interferon compared with placebo in patients with recurrences of genital herpes.

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Patients with recurrent genital herpes were enrolled in the trial after giving written informed consent if they were age 18 and older. All patients were in excellent health and were not receiving concomitant antiviral or immunosuppressive therapy. They were nonpregnant and avoided becoming so while receiving medication. Patients were randomized according to a computer-generated code to receive either recombinant human alpha-2a interferon (Ro 22-8181) at 30 × 10^6 IU/ml (high-dose group) or 10 × 10^6 IU/ml (low-dose group) or placebo (5 mg of albumin per ml of normal saline). Within 24 h of the onset of a recurrence, aqueous solutions of each were applied to all unroofed vesicles with a micropipette applicator with a rubber bulb designed to deliver 25 to 40 μl to each lesion and thereafter six times daily for 5 days. Since each patient had a mean of three lesions treated, the average daily doses applied were 13.5 × 10^6 to 21.6 × 10^6 IU for the high-dose group and 4.5 × 10^6 to 7.2 × 10^6 IU for the low-dose group. Patients were examined daily during the first 5 days to evaluate the clinical appearance of their lesions, the duration of viral shedding, and drug tolerance, as well as on days 7, 9, 11, 13, 15, 18, and 21 and twice weekly thereafter until healing occurred. The lesion number, size, location, and type (macule, papule, vesicle, pustule, ulcer, crusted lesion, or healed lesion) were noted.

All lesions were cultured on days 1 to 5. Lesions were cleansed with saline, swabbed with Dacron applicators, and inoculated into virus transport broth, which was transported to the laboratory on ice. They were cultured on monolayers of mink lung cells which were examined daily for 7 days for the typical cytopathic effects of herpes simplex virus. Isolates were typed using monoclonal antibody. One was type 1, and all the remainder were type 2. Patients were also evaluated for drug toxicity by questioning, examination, and evaluation of a complete blood count, chemistry 23 panel (blood urea nitrogen, serum creatinine, aspartate transaminase, alkaline phosphatase, bilirubin, and serum electrolytes), and urinalysis on days 1, 5, and 21 of the study. Serologic studies to determine whether antibodies to interferon were present were performed on study days 1 and 21. Statistical analyses were performed by analysis of variance (with equivalent nonparametric analyses). The duration of viral shedding was determined from the time a patient entered the study to the first negative culture, the duration of itching or pain was determined from study entry to the cessation of symptoms, the time to crusting was determined from study entry to the crusting of all lesions, and the time to healing was determined from study entry to the complete epithelialization of all lesions.

A total of 94 patients with recurrences of genital herpes were enrolled in this study. Fifty-nine were evaluable for both drug efficacy and safety. Of the 35 patients excluded, 19 were excluded because of negative cultures on day 1, 7 were excluded for missing one or more follow-up visits, 4 were excluded for coexistent skin disease, 3 were excluded for concomitant self-administration of L-lysine, and 2 were

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TABLE 1. Demographics of patients

Characteristic	Interferon		Placebo	P^a
	High dose	Low dose		
Male/female (no.)	9/9	12/10	10/9	0.96
Mean age (yr; range)	31.7 (21–54)	33.3 (18–59)	31.3 (22–65)	0.76
No. on study day 1 with:				
Macules	5	3	3	
Papules	0	1	1	
Vesicles	9	18	13	
Ulcers	4	0	2	
Mean age of lesions on entry into study (h) ± SE	17.3 ± 1.4	19.0 ± 1.4	18.0 ± 1.7	0.73
Mean no. of lesions ± SE	2.9 ± 0.5	3.2 ± 0.4	2.9 ± 0.4	0.82
Mean sum of diam of all lesions (mm) ± SE	6.67 ± 1.9	5.30 ± 0.88	4.13 ± 0.6	0.36
Mean no. of recurrences per yr ± SE	6.2 ± 0.7	8.7 ± 1.2	6.1 ± 0.7	0.09
No. with duration of disease for:				0.86
1 yr	6	10	8	
1 to 2 yr	4	2	4	
More than 2 yr	8	10	7	

[a] P by analysis of variance.

excluded for incorrect application of medication. Of those evaluable for efficacy, 18 received 30×10^6 IU daily (high-dose group), 22 received 10×10^6 IU (low-dose group), and 19 received placebo. All groups were found to be comparable with regard to age, sex, frequency of recurrences, duration of history of genital herpes, and duration of the outbreak at the time of entry into the study, as well as the number, size, and stage of herpetic lesions (Table 1). At the initiation of medication, the type of herpetic lesions was vesicles in more than half the patients in each group.

The mean duration of viral shedding was not significantly different between the three groups (Table 2). The mean duration of pain and itching and the mean number of days to crusting and healing were also not noted to be significantly different.

Local discomfort at the site of application occurred infrequently in all three groups (Table 3). Side effects commonly observed in recipients of parenteral interferon (fever, fatigue, myalgia, and headache) also occurred infrequently in all three groups. Four of eighteen (22%) high-dose interferon recipients experienced gastrointestinal symptoms (nausea and diarrhea), whereas only one low-dose interferon recipient (5%) and no placebo recipients experienced these symptoms ($P < 0.05$ by Cochran-Mantel-Haenszel chi-square). The clinical significance of this observation is unclear, especially since levels of interferon in serum are not detectably increased after topical application of aqueous solutions of alpha-2a interferon (data on file; Hoffmann-La Roche Inc.). Nausea and diarrhea are relatively infrequent clinical adverse effects of therapy with interferon and would have been expected to occur less frequently than fever, headache, and myalgia if systemic absorption of topical interferon had in fact occurred. Leukopenia occurred infrequently in the three groups, and no statistically significant differences were noted. The episodes of leukopenia may have been due to the genital herpes recurrence itself (10). No thrombocytopenia was noted. Antibodies to interferon were not detectable in any patients before or 3 weeks after therapy with alpha-2a interferon.

There are several possible reasons for our failure to observe any beneficial effects of interferon on the duration of viral shedding, the duration of pain or itching, or the time to crusting or healing in patients with recurrences of genital herpes. First, interferon may not be efficacious in treating recurrences of genital herpes (6, 7). However, at least one study (10) has demonstrated some efficacy in genital herpes, and others (3, 4, 8, 16) have demonstrated efficacy in herpes simplex keratitis. Second, the drug may not have been

TABLE 2. Response to treatment

Time to response	Interferon		Placebo	P^a
	High dose	Low dose		
Mean no. of days ± SE of:				
Viral shedding	3.5 ± 0.4	3.1 ± 0.2	4.3 ± 0.7	0.15
Pain	2.7 ± 0.6	1.9 ± 0.3	1.9 ± 0.3	0.25
Itching	3.0 ± 1.0	2.3 ± 0.3	1.9 ± 0.3	0.46
Mean no. of days ± SE to:				
Crusting	2.6 ± 0.2	2.6 ± 0.2	2.7 ± 0.2	0.92
Healing	8.8 ± 1.2	6.8 ± 0.6	7.6 ± 0.7	0.27

[a] P by analysis of variance.

TABLE 3. Adverse reactions

Reaction	No. of patients		
	High-dose interferon	Low-dose interferon	Placebo
Itching or burning	3	2	2
Fatigue	3	2	1
Myalgia	1	2	0
Gastrointestinal symptoms	4[a]	1	0
Headache	3	1	1
Fever	0	0	0
Leukopenia	1	1	2
Thrombocytopenia	0	0	0

[a] $P < 0.05$ by Cochran-Mantel-Haenszel chi-square.

applied early enough in the outbreak to influence its outcome. The mean duration of the lesions before treatment was 17.3 to 19.0 h, respectively, for the high- and low-dose interferon groups, by which time the effect of interferon therapy may be blunted. Previous studies in patients with herpes labialis demonstrated the presence of endogenous interferon in vesicles less than 12 h old, emphasizing the need for early treatment with exogenous interferon, at least in herpes labialis (13). Third, it is possible that the antiproliferative effect of interferon and the unroofing of lesions may have delayed healing as well as the resolution of pain. Finally, an aqueous solution of interferon may not have allowed sufficient penetration of or adherence to the skin in areas of active viral replication. Although interferon in aqueous solution does penetrate cadaver skin in a diffusion chamber model in vitro (data on file; Hoffmann-La Roche Inc.), increases in the levels of interferon in serum were not detected in our patients treated with alpha-2a interferon (data on file; Hoffmann-La Roche Inc.). Superior delivery of drug may be possible by using other vehicles (14). In one clinical trial (9), topical administration of acyclovir in an aqueous cream yielded results superior to those of the identical drug in a polyethylene glycol base. We suggest that subsequent trials use a more efficient topical delivery system without unroofing lesions and that patient self-administration at the earliest sign of an outbreak be used to detect any possible therapeutic benefit of topical interferon in the therapy of genital herpes.

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