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Comparison of Intramuscular Recombinant Alpha Interferon (rIFN-2A) with Topical Acyclovir for the Treatment of First-Episode Herpes Genitalis and Prevention of Recurrences

MYRON J. LEVIN,[1,2,3]* FRANKLYN N. JUDSON,[3,4,5] LAWRENCE ERON,[6] YVONNE J. BRYSON,[7] LAWRENCE COREY,[8] MARTHA MURRAY,[1,2] AND ROBERT R. SCHEER[9]

Pediatric Infectious Diseases Section[1] and Departments of Pediatrics,[2] Medicine,[3] and Preventive Medicine,[4] University of Colorado School of Medicine, Denver, Colorado 80262; Denver Disease Control Service, Denver, Colorado 80204[5]; Division of Infectious Diseases, Fairfax Hospital, Falls Church, Virginia 22003[6]; Pediatric Infectious Disease, Department of Pediatrics, University of California at Los Angeles School of Medicine, Los Angeles, California 90024[7]; Department of Laboratory Medicine, University of Washington, Seattle, Washington 98105[8]; and Hoffmann-La Roche Inc., Nutley, New Jersey 07110[9]

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Intramuscular recombinant alpha interferon (rIFN-2A; 9 million IU given for 5 days during a 9-day treatment period) was compared with topical acyclovir in a double-blind, placebo-controlled trial for the treatment of first-episode genital herpes simplex virus (HSV) infection and for subsequent alteration of the frequency of recurrences. rIFN-2A (within 96 h of onset of the first episode) was not superior to topical acyclovir in a well-matched group of 105 patients. The early use of rIFN-2A also did not alter the frequency or severity of genital HSV recurrences within either the first or second 6 months following therapy. Separate analyses by HSV type and by type of infection (primary versus nonprimary) did not change this conclusion. Furthermore, there was significant toxicity associated with rIFN-2A therapy. rIFN-2A is not indicated for the treatment of genital HSV infections.

Alpha interferon (IFN-α) is efficacious against varicella and herpes zoster in immunocompromised individuals (1, 19). It also can partially suppress cytomegalovirus syndromes in renal transplant recipients (11) and spontaneous reactivation of herpes simplex virus (HSV) in several clinical settings, including reactivation in normal individuals with recurrent herpes genitalis (12, 22). However, because the inhibitory concentrations of IFN-α for HSV and varicella-zoster virus are relatively high (9, 14, 15, 26), nucleoside analogs—for treatment or suppression—are more effective and much less toxic. Consequently, IFN-α has been studied in two additional settings in attempts to extend its value as an antiviral agent. First, in animal models and in the treatment of HSV keratitis in humans, IFN-α has been used to potentiate the antiviral activity of nucleoside analogs (5, 20). A second approach, which is based on the immune-enhancing effects of IFN-α (16, 17, 25, 28–30) as well as on its antiviral properties, is exemplified by the experiment reported here. In this experiment we sought to permanently interfere with the early host-virus relationships by using a recombinant IFN-α, rIFN-2A, to treat first-episode herpes genitalis and thereby decrease the subsequent reactivation frequency.

MATERIALS AND METHODS

Patients were enrolled from July 1983 to January 1985 at four centers: Denver Disease Control Service, Denver, Colo.; The Fairfax Hospital, Falls Church, Va.; University of California at Los Angeles Herpes Research Clinic, Los Angeles; and the University of Washington Herpes Research Clinic at Harborview Medical Center, Seattle. Otherwise healthy individuals, 18 years or older, were eligible for the study if they were entered within 96 h of the onset of lesions characteristic of a primary or nonprimary initial episode of herpes genitalis. Subjects were retained for analysis only if HSV type 1 (HSV-1) or HSV-2 was isolated from skin or mucus membrane lesions. Patients were excluded if they had underlying medical conditions, were pregnant, used inadequate contraception, had abnormal results in pretherapy laboratory tests, had other dermatologic disease in the genital region, or were unable to complete a 1-year follow-up period.

Design. After subjects had given informed consent, a history of recent sexual activity and prodromal symptoms was recorded, and a physical examination was performed. Baseline laboratory tests included complete blood count and differential, platelet count, levels of blood urea nitrogen, glucose, cholesterol, uric acid, calcium, albumin, and creatinine, liver function tests (serum glutamic oxalacetic aminotransferase [SGOT], lactate dehydrogenase, alkaline phosphatase, and serum bilirubin), and urinalysis. A pregnancy test was performed for every female patient. Serum was drawn for HSV antibody determination, and samples from lesions were cultured for HSV.

Subjects were assigned from a computer-generated list of random numbers to receive either intramuscular injections of rIFN-2A (RO 22-8181/001; lot C 120382; Hoffmann-La Roche Inc., Nutley, N.J.) plus a topical placebo ointment (applied every 4 h while awake for 7 days) or an intramuscular placebo plus topical 5% acyclovir ointment (Burroughs Wellcome Co., Research Triangle Park, N.C.). Injections were given the day of entry (day 1) and on days 2, 3, 4 or 5, 7 or 8, and 9. Acetaminophen (650 mg) was given orally at the time of each injection and every 4 h thereafter while patients were awake for 24 h. The dose of rIFN-2A when the study began was 18 million IU per injection. The adverse reaction rate for the first seven patients was unacceptable,

* Corresponding author.

TABLE 1. Clinical features of patients at trial initiation[a]

Treatment	No. of patients	Mean age (yr)	Male/female (no. of patients)	Mean initial symptom severity (no. of patients)				Mean days symptomatic before therapy	Infection (no. of patients)	
				None	Mild	Moderate	Severe		HSV-1	HSV-2
rIFN-2A	53[b]	25.4	17/36	7	14	15	17	1.45	7	46
Topical acyclovir	52	26.4	20/32	9	16	11	16	1.57	11	41

[a] There were no significant differences between the groups of these features.
[b] Includes five patients who received 18 million IU per injection.

and therefore the dose for the subsequent 124 entrants was decreased to 9 million IU per injection.

Patients were given additional acetaminophen as needed for lesion pain, but they were instructed to avoid aspirin, other antiviral agents, and nonsteroidal anti-inflammatory agents during the first episode of herpes genitalis.

All patients were seen on the days of injections and on days 11, 13, 17, 21, and every 4 days thereafter until completely healed. At each visit the distribution, number, and size of lesions were recorded. Lesions were classified as macular, papular, vesicular, pustular, ulcerative, necrotic, crusted, or healed. The areas of individual lesions or groups of lesions were calculated from their diameters, and these were summed to yield the total lesion area. Viral cultures were repeated at each clinic visit.

Patients were questioned at each visit about systemic symptoms and possible adverse reactions to therapy. Laboratory evaluation was repeated on days 5, 9, 13, and 21, and blood for HSV antibody determination was again obtained on day 21.

Virology. Material from genital lesions was obtained with a cotton swab, which was immediately swirled in and held in cold viral transport medium consisting of viral infusion broth, 15% gelatin, and antibiotics. Samples were held at 4°C for less than 72 h, but most were cultured within 4 h. Isolation was attempted in duplicate tubes of human embryonic lung fibroblasts. Cultures were maintained at 37°C for 5 days and observed daily for cytopathic effect. Isolates producing characteristic cytopathic effect were confirmed and typed with fluorescein-labeled monoclonal antibodies (Syva, Palo Alto, Calif.) (24).

Follow-up. Subjects were monitored by monthly telephone calls for 12 months after therapy. The interval between recurrences and the duration and severity of each recurrence (mild, moderate, or severe), as subjectively judged by the patient, were recorded. Patients who developed genital symptoms of uncertain etiology were requested to come to the clinic for examination and viral cultures.

HSV serology. All acute-phase sera were tested by both microneutralization and Western blot (immunoblot) analysis; some follow-up sera were tested by Western blot analysis. Anti-HSV-1 and HSV-2 neutralizing antibody titers were determined by a microneutralization assay similar to one previously described by Rawls et al. (27) and modified by Bernstein et al. (3). Briefly, serial twofold dilutions of heat-inactivated (56°C) serum were mixed with an equal volume of HSV-1 or HSV-2 virus stock at appropriate dilutions in 96-well flat-bottomed microtiter plates. After mixtures were incubated for 37°C for 1 h, trypsinized FS-7 cells (10^4 per well) were added. Plates were incubated for 4 days and then fixed and stained. The presence of anti-HSV-2 activity was determined by using an index described by Rawls et al. (27) and calculated as follows: ([antibody titer to HSV-2 (log 10)]/[antibody titer to HSV-1 (log 10)]) × 100.

Sera exhibiting an HSV-2:HSV-1 index equal to or greater than 85 were considered positive for HSV-2. Western blot analysis was performed as previously described (Bernstein et al. [2]) with antigens prepared from HSV-1- and HSV-2-infected fibroblasts. This method detects antibody responses to individual HSV-1 and HSV-2 polypeptides.

Statistical analysis. The study was designed to detect a 50% difference in outcome between the two study groups with a beta error of 0.80 and an alpha error of 0.05. This required 54 subjects in each study group. The Wilcoxon rank sum test was used in comparing clinical responses between treatments and in comparing some demographic parameters. Categorical data, such as sex, type of virus, and initial level of severity, were compared between treatments by using a chi-square test. The incidence of adverse reactions was compared between treatments by using the Fisher exact test.

RESULTS

Study population. A total of 131 patients with a clinical diagnosis of first-episode genital HSV infection were enrolled. Twenty-six patients did not complete the study; only three patients withdrew because of adverse effects (two in the high-dose rIFN-2A group). The remainder of the patients were excluded because they failed to complete at least 6 months of follow-up. Similar numbers of patients were excluded in each group (12 of 65 who received rIFN-2A, and 14 of 66 who received topical acyclovir). The study groups were similar for all the demographic and prodromal categories analyzed (Table 1).

Effect of rIFN-2A on first-episode genital HSV infection. rIFN-2A was not superior to topical acyclovir for the treatment of first-episode genital HSV infection (Table 2). In fact, the trends in parameters of healing, pain, and virologic responses all favored the nucleoside analog. When primary and nonprimary infections were analyzed separately, the results were similar to those shown in Table 2. Similarly, these conclusions were unchanged when HSV-1 (18 cases) and HSV-2 (87 cases) cases were considered separately.

Adverse effects of rIFN-2A therapy. Reaction rates were analyzed only for the lower dose of 9 million IU per

TABLE 2. Effect of rIFN-2A therapy on outcome of first-episode genital HSV infection[a]

Result	Mean time required (days) ± SD	
	rIFN-2A[b]	Topical acyclovir
Fully crusted	8.79 ± 5.56	7.54 ± 3.73
Skin half-healed	7.08 ± 4.42	6.85 ± 4.10
Skin fully healed	12.58 ± 5.61	11.00 ± 4.61
Cessation of pain	6.34 ± 5.68	5.31 ± 4.02
Negative culture	5.49 ± 3.79	4.14 ± 2.47

[a] No statistically significant differences between treatments were found in these results.
[b] Includes data for five patients who received 18 million IU of rIFN-2A per injection.

TABLE 3. Adverse reactions

Reaction	No. of patients		P[a]
	rIFN-A (n = 58)	Topical acyclovir (n = 66)	
Visual disturbance	17	7	0.012
Dizziness	12	2	0.003
Diarrhea	11	13	1.000
Nausea	27	17	0.024
Vomiting	11	5	0.067
Anorexia	29	19	0.017
Sweating	8	0	0.002
Fever (>37.5°C)	47	14	<0.001
Fatigue	43	34	0.015
Chills	44	16	<0.001
Headache	40	29	0.007
Myalgia	46	30	<0.001
Paresthesia	17	16	0.548
Neutropenia	25	5	<0.001
Elevated SGOT	12	6	0.078

[a] Two-sided comparisons.

injection. A large number of symptoms appeared to be related to therapy (Table 3). It was assumed that symptoms were due to rIFN-2A rather than to first-episode HSV infection when they were more common in the rIFN-2A recipients than in the topical-acyclovir recipients. Especially distressing for patients were symptoms of anorexia, nausea, fever, chills, fatigue, and headache. SGOT levels (normal, 35 IU/liter) exceeded 100 IU/liter in only two rIFN-2A recipients. In all cases, liver function returned to normal after cessation of therapy. Most consistent was the depressive effect of rIFN-2A on neutrophil count, with 45% of rIFN-2A recipients experiencing low counts (defined as less than 1,830 neutrophils per ml), compared with 8% of acyclovir recipients. No effects on platelets or lymphocytes were noted. The neutrophil count returned to the normal range within 3 days of stopping rIFN-2A therapy. Of interest was the reactivation of severe type 1 orofacial HSV infection in three patients coincident with rIFN-2A therapy for type 2 genital HSV infection.

Effect of rIFN-2A on frequency of HSV recurrences. Early therapy of first-episode genital HSV infection with rIFN-2A did not decrease the frequency of recurrences (Table 4). In the acyclovir group, recurrences occurred at a frequency similar to that reported previously for untreated patients (7, 8, 21). rIFN-2A did not reduce the rates of either early or late recurrences or their severity. Separate analyses by HSV type and by type of infection (primary versus nonprimary) did not change these conclusions.

DISCUSSION

IFN-α has in vitro activity against HSV (9, 14, 15, 26) and partially inhibits the reactivation of HSV latent in sensory ganglia which innervate oral and genital sites (12, 22). The first preparations of IFN-α were made from cultured human leukocytes and were therefore relatively expensive and scarce. The cloning of a family of genes which code for at least five distinct polypeptides present in naturally produced IFN-α has remedied these problems and facilitated additional trials (10, 31).

We undertook a trial with one of these recombinant IFN-α's, rIFN-2A, to assess the relative efficacy of rIFN-2A and topical acyclovir in the treatment of first-episode genital HSV infection. Oral acyclovir was not available when patients were entered into this trial. While we demonstrated no significant differences between these two therapies, topical acyclovir was superior to rIFN-2A in all categories evaluated (Table 2). Ethical considerations precluded the inclusion of a placebo group. However, comparison with historical controls does suggest that both rIFN-2A and topical acyclovir accelerated crusting, healing, disappearance of pain, and cessation of virus shedding (4, 6–8, 21).

While our study of first-episode genital HSV infections was in progress, two additional IFN-α therapy trials were completed. One trial, which used partially purified native human IFN-α, demonstrated a significant decrease in virus shedding and a trend toward faster healing (23). Pain was not decreased. A second trial used a recombinant IFN-α, rIFN-2B, which differs from rIFN-2A by a single amino acid (18). Although no therapeutic effect was noted with rIFN-2B, the number of patients treated was small and treatment was started as late as 5 days after onset of symptoms. rIFN-2A has also been used to treat recurrent genital HSV infections and reduced healing time and pain (13).

It is clear from our study with rIFN-2A, and from the studies cited above, that any beneficial effects of IFN-α therapy are associated with significant clinical and laboratory side effects. Since oral acyclovir is more efficacious than topical acyclovir and is virtually without side effects, neither rIFN-2A nor any other IFN-α appears to be suitable therapy for first-episode genital HSV infection.

Anticipating these factors, we also examined an additional hypothesis: that the immune-enhancing properties of rIFN-2A would interfere with the normal mechanisms which establish or maintain latency. This required initiation of therapy soon after the onset of symptoms. It previously had been demonstrated that rIFN-2A did not alter established HSV latency, since administration of rIFN-2A for 3 months to patients with recurrent genital HSV infection did not decrease recurrence frequency (12). Unfortunately, we found the same result when rIFN-2A therapy was begun within 96 h of the first episode of genital HSV infection (Table 4). The failure to alter recurrence frequency applied equally to patients with primary and non-primary first-episode infections and to those with HSV-1 and HSV-2 infections. Our results confirm those obtained with native IFN-α and rIFN-2B, although the power of the latter study is

TABLE 4. Effect of therapy on recurrences[a]

Treatment	Mean no. of recurrences ± SD			Mean lesion duration (days) ± SD	Mean lesion severity score[b] ± SD
	Per mo	First 6 mo	Second 6 mo		
rIFN-2A[c]	0.39 ± 0.42	2.25 ± 2.72	2.39 ± 2.66	6.60 ± 3.28	1.49 ± 0.44
Topical acyclovir	0.33 ± 0.41	2.00 ± 2.82	1.80 ± 2.62	6.66 ± 2.98	1.43 ± 0.47

[a] No significant differences were found between treatment groups in recurrences.
[b] 1, Mild; 2, moderate; 3, severe.
[c] Includes data for five patients who received 18 million IU per injection.

decreased by the small number of patients and a longer delay before initiation of therapy (18, 23).

Since this study was completed, oral acyclovir has been shown to be superior to topical acyclovir in the treatment of first-episode genital HSV infections. Because rIFN-2A did not decrease recurrences after first episodes, we conclude that early administration of oral acyclovir is the optimal treatment in this situation.

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