

$$6 \overline{) 180} \\ 30$$

N = 180 60/group.

①

②
ACV

③

50. BOTH
all Placebo tid

5mg/kg^{II} tid x5

IFA
18 x 10⁶ IM x5

F/U 12 mo

indicator ↓ freq. of recurrence

♂ or ♀

96 hr IN or OUT

HSV1 or 2 isolated once

contraceptive

WBC 3500/1500 plate 100,000

NO prior IFA.

Must be available 12 mos.

2yr study, 3yr to complete

F/U 0 1-5 6 or 7 8 or 9 10 or 11 / 12 or 13 16 or 17 or 18

20 or 21 or 22

9 4 until healed

telephone q. mo.

clinical studies center.

1. Clin studies center

2. heparin lock

3. 5mg/kg tid x5 → altered freq.

18 x 10⁶ = altered freq.

Comparison of the Efficacy of Intravenous Acyclovir, Intramuscular
Recombinant Leukocyte A Interferon (Ro 22-8181/001), Versus the Combination
of the Two Agents in the Therapy of Primary/Initial Herpes Genitalis

PROTOCOL NO: 2661

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Comparison of the Efficacy of Intravenous Acyclovir, Intramuscular
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Combination of the Two Agents in the Therapy of
Primary/Initial Herpes Genitalis

Date: November, 1983

Phase: II

Protocol No.: 2661

HLR Test Drug

Recombinant Leukocyte A
Interferon (Ro 22-8181/001;
rIFN- α A)

Dose Form and Strength

5 ml vials containing lyophilized
powder consisting of 18×10^6
monomeric units/ml of Ro 22-8181/001,
5 mg/ml of human serum albumin, and
9 mg/ml of sodium chloride.

IND NO. #BB1531

Placebo to match Recombinant
Leukocyte A Interferon
(Ro 22-8181; rIFN- α A)

5 ml vials containing lyophilized
powder consisting of 9 mg/ml sodium
chloride, and 5 mg/ml human serum
albumin.

Comparative Drug

Acyclovir Powder (Zovirax®)
for intravenous use
Placebo to match acyclovir (Zovirax®)
for intravenous use

SYNOPSIS

This is a multicenter, prospective, randomized, double-blind study with 2 parallel groups of 60 patients/arm for a total of 180 patients. This study is designed to determine whether the efficacy of the combination of intramuscular Recombinant Leukocyte A Interferon and intravenous acyclovir (Zovirax®) is superior to therapy with either intravenous acyclovir or intramuscular Recombinant Leukocyte A Interferon (Ro 22-8181/001; rIFN- α A) alone in patients with an initial or primary episode of genital Herpes Simplex infection. The patients will receive 5 mg/kg intravenous acyclovir three times daily and intramuscular placebo once daily, or intravenous placebo three times daily and 18×10^6 units intramuscular recombinant Leukocyte A interferon once daily or both drugs for five days. Patients will be followed during the primary episode and for recurrences for a total of 12 months. History and physical examination, serum chemistries, CBC, virus cultures, and anti-interferon antibodies will be monitored. Efficacy of therapy will be evaluated in terms of the rate of healing and virus shedding from lesions during the initial episode. The major indicator of increased efficacy of the combination of IV acyclovir and IM rIFN- α A will be whether the incidence and severity of recurrent episodes of Herpes Simplex genitalis occurring after the primary or initial episode can be diminished.

BACKGROUND:

Genital herpes is a sexually transmitted infection caused most frequently by Herpes Simplex virus (HSV) Type 2 and less commonly by HSV Type 1. Primary or initial episodes of genital HSV infections are often debilitating with widespread cutaneous involvement and frequent systemic symptomatology. Involvement of the female genital tract causes painful vesicles and ulcers of the vulva and vagina and infection of the cervix. In the male, painful vesicles and ulcers occur on the glans penis, prepuce, and shaft of the penis. Bilateral inguinal lymphadenopathy may be present in both sexes and, in primary infections, it is frequently painful. Dysuria is a common complaint in initial herpes genitalis in women. About 50% of patients with either primary or recurrent genital herpes complain of systemic symptoms, including neuralgia, malaise and fever.¹ In primary genital infections many lesions may appear and they are often symptomatic for approximately 3 weeks. Extragenital lesions can result from contamination of fingers by infected secretions and passage of virus through skin excoriations. Viral shedding lasts for 11-13 days.¹

There are several complications of primary or initial genital herpes simplex infections. Approximately 1% of the patients develop aseptic meningitis and some of these patients may require hospitalization for evaluation and therapy. CSF pleocytosis is common but viral cultures are routinely negative. Urinary retention requiring catheterization may, in rare cases, necessitate hospitalization for therapy. In general, however, hospitalization is not necessary for the majority of patients utilizing currently approved therapeutic modalities.

Recurrence of genital herpes is a major problem as noted in a study by Corey and colleagues where 55% of the patients with primary HSV-1 infection studied and 88% of the patients with primary HSV-2 infections recurred following a first episode.² The rate of recurrences is considerably higher in patients infected with HSV-2 than in those with primary infection due to HSV-1.²

Recurrent genital herpes usually results from reactivation of endogenous HSV-2 which remains latent in sacral sensory ganglia. It is presently unknown what percentage (if any) of recurrences are due to reinfection as opposed to reactivation of latent virus. In recurrent disease resolution of cutaneous lesions occurs in approximately 9-10 days, with virus shedding lasting about 4-5 days.¹ Symptoms associated with recurrent disease are usually milder in intensity. In recurrent disease, some patients experience prodromal symptoms prior to the onset of a clinical recurrence. Since the major morbidity of Herpes genitalis in certain patients is related to frequent recurrence of infection a major goal of therapeutic intervention has been to alter subsequent recurrence rates.

Experimental therapy of primary and recurrent genital herpes simplex infections with a large number of agents have demonstrated that the majority are ineffective.^{3,4,5} Topical acyclovir has been

demonstrated to be clinically effective in primary but not in recurrent episodes of Herpes genitalis.^{6,7} Although clinical benefit has been demonstrated with topical acyclovir therapy of primary Herpes genitalis this medication has not been shown to diminish subsequent rates of recurrence.

Intravenous acyclovir has been approved recently for therapy of severe primary or initial genital herpes simplex infections.⁸ Such therapy requires either inpatient or outpatient facilities for intravenous therapy. Intravenous acyclovir has been shown to be safe and is effective in diminishing the duration of viral shedding and promoting healing in patients with primary herpes genitalis. The effect of intravenous acyclovir on the rate of recurrences after a primary or initial episode has not yet been definitively documented.

Oral acyclovir has also been shown to be an effective therapeutic modality in patients with initial episodes of herpes genitalis.⁹ In this study no significant effect was observed on the incidence of subsequent recurrent episodes.⁹ Despite these results, oral acyclovir has not yet been approved for clinical use in patients with primary herpes genitalis. Studies have also documented that oral acyclovir when taken daily is effective in suppressing recurrent episodes.¹⁰ When therapy is discontinued this effect in preventing recurrences is lost and therefore it appears that long term therapy may be required in patients with frequent recurrences. The long term effects of therapy with acyclovir are at present unknown.

Interferon - Immunologic Effects

Interferons have been demonstrated to have varied and potent effects on the immune system in vitro and in vivo in experimental animals. Mechanisms by which interferon might potentially influence immunological defenses against viruses in vivo include: (a) stimulation of phagocytosis resulting in increased neutralization of extracellular viruses; (b) stimulation of antibody dependent cellular cytotoxicity (ADCC) and (c) stimulation of natural killer cell maturation, division or function. It has been reported that interferon may suppress de novo antibody production.¹¹ Conflicting experimental results have been noted with respect to interferon's effect(s) on experimental graft versus host disease (GVHD).

The effects of therapy with rIFN- α A on immunologic parameters have been varied. Recombinant Leukocyte A Interferon has been shown to enhance monocyte mediated ADCC and tumor cell cytostasis in the majority of patients tested. No dose response effect was reported in these studies and the relevance of these in vitro parameters to in vivo immunologic function has not been determined. NK cell function was unchanged or diminished in the majority of patients treated with multiple doses of rIFN- α A. Thus rIFN- α A has been

demonstrated to suppress certain immune parameters in patients. Its effects when administered in combination with either glucocorticosteroids or cytotoxic immunosuppressive agents is unknown. The effects of rIFN- α A on graft rejection and GVHD are also not clearly delineated at present. Our present understanding of and inability to evaluate human immunologic competence have impaired further interpretation of presently available data. No definitive studies on the effects of rIFN- α A administered to normals or patients with Herpes genitalis have been performed.

Drug Interactions

Preliminary studies suggest that rIFN- α A and other human interferons depress the cytochrome P-450 system. Thus serum levels of other medications which either require activation by this metabolic pathway or which are metabolized via this mechanism may be affected. Particular attention should be paid to the use of concomitant medication in patients being treated with rIFN- α A.

In vitro, the activity of interferon has been shown to be decreased by substances which inhibit cyclooxygenase.¹² Therefore, patients should not take medicines such as aspirin and other non-steroidal anti-inflammatory agents (NSAIA) which inhibit cyclooxygenase. This potential inhibition of the activity of rIFN- α A with NSAIA has not been adequately studied in vivo. Other studies with non-recombinant human leukocyte interferon and with rIFN- α A suggest that this interaction may not be clinically important.¹³ In vitro and in vivo studies with rIFN- α A have documented that acetaminophen does not interfere with its antiviral properties whereas acetylsalicylic acid and idomethacin may in specific situations.¹⁴

Interferon - Preclinical Studies

A) EFFICACY

Leukocyte-derived interferon has potent antiviral activity in vitro and in vivo. Recombinant human leukocyte A interferon has been produced in transformed *E. coli* and has been shown to have similar in vitro and in vivo activity.¹⁵ The antiviral effect of interferon in vitro is thought to be mediated at several steps on transcription of viral DNA or RNA, translation of viral nucleic acid into protein, and with some viruses on their assembly.¹⁶ The specific activity of rIFN- α A in human cells is $2-4 \times 10^8$ U/mg protein when measured by an antiviral assay utilizing vesicular stomatitis virus (VSV). The sensitivity of several viruses to rIFN- α A was measured in human cells with the following results: Semliki Forest virus was the most sensitive (its inhibitory dose was 0.2 U/ml) followed by EMC virus (1.1 U/ml), Rhinovirus (type 1A 3.0 U/ml), HSV-1 (14 U/ml), and HSV-2 (85 U/ml).¹⁷

Ro 22-8181 (rIFN- α A) protected monkeys from fatal infections with EMC virus and Simian Varicella virus. In one experiment, rabbit eyes challenged topically with Herpes Simplex were protected against corneal epithelial damage mediated by virus when rIFN- α A was administered topically.¹⁸ Combination of rIFN- α A or α D and Trifluorothymidine (TFT) was superior to either agent alone in rabbits with Herpes Keratitis.¹⁹ rIFN- α A, which was demonstrated to be an active antiviral agent on guinea pig cells in vitro, has been shown to be active in the guinea pig model of genital herpes simplex infection.²⁰ In these experiments rIFN- α A was effective in treating primary genital HSV-2 infections in guinea pigs as manifested by diminished viral shedding and hastening the rate of healing of lesions. In addition early therapy significantly reduced the frequency of subsequent recurrent episodes.

rIFN- α A/D, a hybrid molecule derived from DNA coding for rIFN- α A and rIFN- α D, has been shown to have activity in mice. In a model utilizing neonatal mice infected with herpes simplex virus, rIFN- α A/D was shown to be effective in decreasing the mortality rate of this lethal disease. Therapy begun prior to virus inoculation was demonstrated to be superior to therapy begun at times after infection of these experimental animals.²¹

B) TOLERANCE

rIFN- α A has exhibited a substantial degree of species specificity. This factor has made pre-clinical animal toxicological evaluation difficult. The adverse effects noted in various animal species have not mimicked the experience gained in clinical trials. Despite this limitation, reproduction physiology and teratology studies in sub-human primates has begun. Preliminary findings include:
(a) alterations of the periodicity of the menstrual cycle;
(b) intermenstrual bleeding; and (c) an increased rate of abortions.²² Further information is detailed in the IDB and supplements.

Clinical Studies with Natural and Recombinant Leukocyte Interferon in Viral Infections

Antiviral activity of interferon has been reported in the following clinical situations:

- 1) Prevention of cold symptoms after intranasal rhinovirus challenge with either natural²³ or recombinant interferon²⁴
- 2) Therapy of acute HSV keratitis either alone²⁵ or in combination with other antiviral agents.^{26,27} In these two studies utilizing non-recombinant human interferon α in combination with either TFT or acyclovir (ACV) it was demonstrated that combination therapy was significantly superior to either agent alone.

- 3) Therapy of herpes zoster in immunosuppressed cancer patients to prevent dissemination.²⁸
- 4) Prevention of reactivation of herpes labialis after trigeminal ganglion surgery.²⁹
- 5) Therapy with leukocyte interferon with or without adenine arabinoside in hepatitis B infections.^{30,31}
- 6) Therapy of varicella in children with cancer.³²

Studies with leukocyte and recombinant interferon in which dosage has been evaluated suggest that antiviral efficacy may increase as the dose increases. In a study of herpes zoster in immunosuppressed cancer patients a dose of 36×10^6 units/day of human leukocyte interferon prevented dissemination of lesions from the primary dermatome.²⁸ A reduction in both pain and virus shedding was also observed in this study.²⁸ Recent studies utilizing daily or twice daily dosing of patients with chronic hepatitis B virus infection demonstrated that higher doses of rIFN α A suppressed viral markers to a greater extent than did lower doses.³³

Clinical Studies with Recombinant Interferon - Tolerance & Side Effects:

In Phase I studies, rIFN- α A has been tested for safety and tolerance in over 300 patients. In addition over 600 patients have been treated with Ro 22-8181 in Phase II studies.

The most frequently observed side effects found in the Phase I studies included fever, fatigue, and flu-like systemic symptoms (headache, chills, myalgias). Gastrointestinal disturbances (anorexia, nausea, vomiting, and diarrhea) were sporadic but increased incidence occurred at doses of 36×10^6 U and above. Fatigue, anorexia, and weight loss were the dose limiting side effects in the Phase II studies. The hematologic abnormalities included transient leukopenia and thrombocytopenia.

Neurologic side effects were less frequently observed. The neurologic disturbances observed are divided into those involving the peripheral nervous system (transient and reversible mild numbness or paresthesias of fingers or toes³⁴) and the central nervous system (confusion, disorientation, cognitive difficulties, and disturbances of the level of consciousness³⁴). The CNS side effects were generally seen at doses greater than 36×10^6 U/day.

The most frequently affected parameter of liver function at the higher interferon dose levels was transient elevation of SGOT with no demonstrable compromise of hepatic synthetic functions. Discontinuation of interferon resulted in normalization of SGOT levels.

Signs of renal impairment were minimal. Significant proteinuria was seen in a few patients. These cases include one patient who developed nephrotic syndrome and acute renal failure.

Clinically significant cardiovascular side effects have been infrequent and generally occur in patients with pre-existing cardiac disease. Many patients have experienced asymptomatic hypotension and transient arrhythmias. Exertional angina pectoris has been reported but the patients have had previous histories of hypertension and coronary artery disease. One patient with a prior history of myocardial infarction and stable angina developed a cardiac arrest and expired.

Further details will be found in the Investigational Drug Brochure and its supplements³⁵.

Approximately 10% of patients treated with parenteral rIFN- α A have developed low levels of neutralizing antibodies to it in convalescent sera. The antibodies in most patients had specificity for rIFN- α A but in three patients antibody reacted broadly with other subspecies of α interferon tested. The predominant specificity of the antibodies induced was, however, for rIFN- α A and not other subspecies of α interferons.³⁵

Limited information is available on the tolerance of combined therapy with acyclovir (Zovirax®) and interferon.³⁶ Some neurotoxicity has been reported with parenteral acyclovir treatment after bone marrow transplantation.³⁷ For this reason particular attention must be paid to the possibility of either unexpected toxicities or worsening of known adverse experiences due to either drug alone in patients treated on this protocol.

Pharmacokinetics of rIFN- α A:

Pharmacokinetic data are outlined in detail in the Investigational Drug Brochure, a copy of which will be provided by the sponsor.³⁸

Rationale:

At present there is no known therapy which effectively prevents recurrences of genital herpes simplex infections after primary infection. No effect on the incidence of recurrences was documented when primary or initial episodes of herpes genitalis were treated with either oral⁹ or topical⁷ acyclovir. In vitro studies have demonstrated either an additive or synergistic antiviral effect between interferon and other antiviral agents.³⁹ The demonstration of additive or synergistic effects of interferon and other antiviral agents may be explicable based on their disparate modes of action.

More recently synergistic or additive effects have been demonstrated between human leukocyte (α) interferon and acyclovir in vitro against HSV-I, HSV-II, CMV and VZV.^{40,41,42} Whether such in vitro effects will be translated into documented clinical benefit remains to be determined. Studies of the effect of acyclovir, rIFN- α A, and passively transferred human leukocytes in mice infected with HSV suggest that combinations of these therapeutic modalities are superior to any of these treatments alone.⁴³ It has recently been reported that thymidine kinase in mammalian cells may be necessary for the action of interferons.⁴⁴ It is unclear whether the viral-encoded TK is either sufficient or required for the development of the antiviral state after interferon administration.⁴⁴

The development of resistance to acyclovir in a variety of clinical isolates and laboratory strains of herpes simplex viruses has been documented.⁴⁵ Clinical isolates of ACV-resistant HSV have been demonstrated to be sensitive to rIFN- α A.⁴⁶ Since acyclovir is phosphorylated to its active form predominantly in HSV-infected cells, the development and/or selection of HSV mutants deficient in thymidine kinase leads to the development of relative resistance to acyclovir. The clinical significance of the development of resistance of HSV to acyclovir is uncertain at present but individual patients with ACV-resistant HSV do not respond to therapy with ACV in vivo.⁴⁵ It is possible that the emergence of a sizeable percentage of isolates resistant to this agent may ultimately limit its usefulness and also the utility of other agents requiring phosphorylation by TK. Agents which act without modification to inhibit the viral DNA polymerase would theoretically still be useful against such mutant viruses.

In addition to the possibility that the combination of interferon and acyclovir might be more effective than either alone, it is also possible that combination therapy may prevent or delay the emergence of acyclovir resistant mutants. If either additivity of clinical effect or the prevention of acyclovir resistance can be demonstrated, the planning of future therapy for a variety herpes simplex virus infections could be expedited.

Since recurrent episodes are the major cause of morbidity in this disease, this study is undertaken to determine whether the combination of intramuscular Recombinant Leukocyte A Interferon and intravenous acyclovir is superior to therapy with either intravenous acyclovir or intramuscular Recombinant Leukocyte A Interferon alone in altering the clinical course of primary/initial genital herpes simplex infection and in preventing recurrences following the treated episode.

I. Objective of Study

To determine whether the efficacy of the combination of intramuscular Recombinant Leukocyte A Interferon and intravenous acyclovir is superior to therapy with either intravenous acyclovir or intramuscular Recombinant Leukocyte A Interferon alone in patients with a primary or initial episode of Herpes Genitalis in decreasing the incidence of recurrent episodes.

II. Experimental Plan

A. Patient Selection

1. Total number of cases: 180
2. Age: 18 years of age or older
3. Sex: Male and Female
4. Type of patient: Patients with a severe episode of primary or initial genital herpes will be considered for entry. Otherwise healthy patients presenting within 96 hours of the onset of lesions in primary or initial episode of Herpes genitalis (determined by medical history and clinical judgement). Patients may be treated as inpatients or outpatients at the discretion of the principal investigator.
5. Diagnostic Criteria: HSV-1 or HSV-2 must be isolated from a typical lesion at least once during the initial episode, preferably at baseline.

B. Type of Patients and Diseases to be Excluded:

1. Women of childbearing potential will be excluded unless using effective contraception during the interferon treatment period. Women who are pregnant and lactating women will also be excluded. A pregnancy test will be performed on each premenopausal female at entry into the study and drug will be administered only to those patients with a negative test.
2. Fertile men unless using effective contraception during the treatment period.
3. Patients who are immunosuppressed either iatrogenically or by their underlying illness (cancer, acquired immunodeficiency, connective tissue disorder).

4. Patients with a WBC count less than $3500/\text{mm}^3$.
5. Patients with a granulocyte count less than $1500/\text{mm}^3$.
6. Patients with a platelet count less than $100,000/\text{mm}^3$.
7. Patients with any significant history of cardiac disease including myocardial infarction, angina, arrhythmias.
8. Patients with any significant renal, hepatic, pulmonary, neurological or other organ dysfunction, or significant mental or emotional instability. This exclusion is meant to exclude all patients with a history of, physical findings suggestive of, or laboratory abnormalities attributable to disease of these organ systems.
9. Patients who are not likely to be available for the entire study, including 12 months of follow-up.
10. Patients with active dermatologic disease other than Herpes Genitalis including secondary bacterial infection of Herpes Genitalis.
11. Any patient having received interferon previously for any indication.

C. Drugs to be Excluded During the Study

1. Aspirin
2. Other non-steroidal anti-inflammatory agents
3. Other antiviral drugs (for two weeks prior to entry, during treatment, and if possible during the entire period of follow-up).

Note: Examples of drugs which may be administered concomitantly for pain relief are acetaminophen, propoxyphene, and narcotic analgesics.

D. Control Methods

1. Double-blind
2. Parallel Groups
3. Computer-generated randomized code

E. Drug Treatment Plan

1. Study Design

Patients will be assigned randomly to one of three treatment arms and be treated for 5 consecutive days with either:

- 1) 18×10^6 units of intramuscular rIFN- α A once daily + IV placebo every 8 hours or
- 2) 18×10^6 units of intramuscular rIFN- α A + 5mg/Kg IV acyclovir every 8 hours or
- 3) Placebo for intramuscular interferon + 5mg/Kg IV acyclovir every 8 hours.

Note: See attached package insert for IV acyclovir (Appendix D). This therapy may be administered either as an inpatient or an outpatient. This medication will be coded and will be supplied by the sponsor.

Each vial will bear the code corresponding to the patient to be treated and each treatment will require intramuscular injection of one vial. The patient should take 650 mg acetaminophen at the time of each injection and every 4 hours thereafter, while awake, on the days of intramuscular therapy.

2. Dose Modification

In the event of drug-related toxicity or intolerance, the dose of IM medication may be reduced to one-half. After this dose reduction the patient may continue to receive 50% of the initial dosage unless unacceptable toxicity occurs. This dosage reduction must be clearly noted on the case report form. If toxicity is thought to be due to acyclovir, or to the combination of rIFN- α A and acyclovir, clinical judgment should be used to treat the patient.

3. Coding of Medication

Vials of interferon and placebo and of acyclovir (Zovirax®) and placebo will be supplied in advance and identity of contents will be coded and unknown to the patient and investigator. The code will be retained by Hoffmann-La Roche Inc. The identity

of the vial contents is disclosed within the detachable portion of the labels. If the responsible physician deems the information essential for the appropriate management of the patient, he may open this "tear-off" portion which will reveal the name and dosage of the test drug. No label should be opened except in an emergency. In such a case, the breaking of the code must be clearly explained in writing on the case report form by the principal investigator. In such cases results obtained will be evaluated with respect to patient safety, but the patient will not be included in the analysis of efficacy.

Assignment of patients to their specific groups will be determined by means of a computer-generated randomized code. Patients must be assigned a patient code number in sequential numerical order as they enter the study. This information will be recorded on the Drug Dispensing Log. The tear-off portion of the labels will be detached from the box and attached to the appropriate spaces on the case report form. Upon termination of the study, all unused coded medication will be returned to Hoffmann-La Roche, Inc.

4. Duration of Treatment

Intramuscular injections of Ro 22-8181/001 or placebo once daily on days 1 through 5. Intravenous acyclovir (Zovirax®) 5 mg/kg or intravenous placebo every eight hours daily for 5 consecutive days. Each patient will be observed for a total of 12 months after therapy of the primary or initial episode of genital herpes simplex infection.

F. Duration of the Study:

The anticipated accrual of patients is such that in 6 institutions all patients could be enrolled in approximately 24 months and the study completed in approximately 36 months.

G. Parameters to be Measured

(see Study Flow Chart, Appendix A. page 22)

<u>Parameters</u>	<u>Frequency</u>
1. Hepatitis B surface antigen screening	Baseline, and repeated if patient receives a blood product or is exposed to Hepatitis B. (see Appendix C, page 25).
2. Pregnancy test on urine of pre-menopausal females	Baseline (No therapy should be administered unless this test is negative).
3. History and physical examination.	Baseline, if indicated during the course of the study and day 20, 21 or 22. 12 months, if indicated.
4. Vital signs	Baseline; pre-injection on day 2 to 5. Follow-up at day 20, 21, or 22.
5. Examination of the primary/initial herpes genitalis infection:	
a) precise initial distribution and number of lesions and appearance of new lesions by day of study	
b) severity of lesions by morphological class (i.e. 0-macule, 1-papule, 2-vesicle, 3-pustule, 4-ulcer, 5-crust, 6-healed, 7-deep necrotic lesion).	Baseline; daily during the first 5 days of the study; then, days 6 or 7; 8 or 9; 10 or 11; and if lesions persist, days 12 or 13; 16, 17, or 18; 20, 21 or 22; and every 4 days until lesions are healed.
c) Size of each lesion determined by the greatest diameter in mm.	
d) duration of lesions to crusting and healing	
e) severity and duration of pain will be rated on a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe)	

<u>Parameters</u>	<u>Frequency</u>
f) global status of the disease will be rated on a 3 point scale (mild, moderate, severe)	Baseline; daily during the first 5 days of the study; then, days 6 or 7; 8 or 9; 10 or 11; and if lesions persist, days 12 or 13; 16, 17, or 18; 20, 21 or 22; and every 4 days until all lesions are completely healed.
g) evaluation of the signs and symptomatology of the disease or treatment including any pain, itching, paresthesias, fever, chills, nausea, vomiting, headache, stiff neck, photophobia, myalgia, fatigue, malaise, anorexia, diarrhea, constipation, dysuria, inguinal adenopathy, vaginal or urethral discharge, urine retention, and hypotension.	
6. Examination of intramuscular and intravenous sites for local tolerance (i.e. tenderness, erythema, edema, and rash).	Baseline, daily through day 5; follow-up at each visit if necessary.
7. History of Herpes genitalis recurrences with special attention to the duration and clinical findings in each episode of genital herpes.	Monthly telephone or post-card follow-up. Patients with a recurrence of Herpes genitalis during the period of follow-up will be seen at least once during each recurrence.
8. Laboratory tests to include:	
a. CBC with differential and Platelets.	Baseline; days 3; 5; 8 or 9; and 20, 21, or 22.
b. SMA-12 which includes alkaline phosphatase, SGOT, total bilirubin, blood sugar, serum cholesterol, total protein, uric acid, phosphorus, calcium, serum albumin, LDH, and serum creatinine.	Baseline; days 3; 5; 8 or 9; and 20, 21, or 22.

<u>Parameters</u>	<u>Frequency</u>
c. Urinalysis.	Baseline; days 3; 5; 8 or 9; and 20, 21, or 22.
d. Serum Interferon antibody level. (See Appendix C, p. 25.)	Baseline (prior to administration of test drug) and day 20, 21, or 22.
e. Virus identification (HSV -1 or -2)	Baseline or at least once during the initial episode.
f. Viral culture	Baseline; days 2,3,4,5; 6 or 7; 8 or 9; 10 or 11; 12 or 13; 16, 17, or 18; 20, 21 or 22; and if lesions persist every four days thereafter. When healing of all lesions is complete no further cultures need be taken.
g. HSV antibody titer (Type 1 and 2)	Baseline and day 20, 21, or 22.

H. Adverse Reactions:

Should a serious adverse reaction occur, the patient should present himself to an Emergency department and contact the principal investigator immediately. All serious or unusual reactions must be reported to Hoffman-La Roche.

All adverse reactions encountered during this study will be carefully evaluated and treated in a medically appropriate manner. Interferon toxicity (as outlined in the Investigational Drug Brochure and supplements) will be evaluated regarding the severity of the toxicity on hematologic and hepatic functions as well as clinical parameters of fever, fatigue, gastrointestinal intolerance, numbness, paresthesias, and other evidence of neurological toxicity, etc. Whenever possible toxicity and clinical side effects will be graded as mild, moderate, or severe and reported in detail on the Case Report Form.

Criteria for determining the relationship of clinical adverse reactions to the test drug will be found in Appendix B, page 23.

All patients exhibiting toxicity should be treated as outlined in Table I.

TABLE I. MANAGEMENT OF INTERFERON TOXICITY

Category of Adverse Effects	Decision Criteria	Severity of Adverse Effect	Clinical Management
<u>Hematologic</u>			
a) WBC	<3000	Moderate	1. De-escalate to 50% of dose of IM medication. 2. If toxicity continues <u>STOP</u> drug completely
	<2000/mm ³	Severe	<u>STOP</u> drug completely
b) Granulocyte	<1500/mm ³	Moderate	1. De-escalate to 50% of dose of IM medication. 2. If toxicity continues <u>STOP</u> drug completely
	<1000/mm ³	Severe	<u>STOP</u> drug completely
c) Platelets	<100,000/mm ³	Moderate	1. De-escalate to 50% of dose of IM medication. 2. If toxicity continues <u>STOP</u> drug completely
	<75,000/mm ³	Severe	<u>STOP</u> drug completely
<u>Hepatic - SGOT</u>	>200 u/dl	Severe	<u>STOP</u> drug completely
<u>Renal</u>			
a) Creatinine	>2x baseline	Severe	<u>STOP</u> drug completely
b) Proteinuria	>3+	Severe	<u>STOP</u> drug completely
<u>Neurological</u>	Fatigue and/or paresthesias tolerated by patient.	Moderate	1. De-escalate to 50% of dose of IM medication. 2. If toxicity continues <u>STOP</u> drug completely
	Confusion, disorientation, cognitive dysfunction, etc.	Severe	<u>STOP THERAPY</u>

Adverse experiences, which in the principal investigator's opinion are related to intravenous acyclovir, will be treated appropriately as outlined in the package insert or by using clinical judgment. No significant increased toxicity has been noted in patients treated with acyclovir and interferon³⁶, but an increased incidence and/or severity of neurotoxicity was seen in patients treated with Ara A and interferon in combination.⁴⁷ Thus careful attention should be paid both to any expected or unexpected potential adverse experiences.

ANY DEATH, ANY UNUSUAL OR SERIOUS REACTION, OR ANY UNUSUAL FREQUENCY OF REACTIONS WILL BE REPORTED PROMPTLY BY TELEPHONE TO THIS DEPARTMENT EVEN THOUGH THE EXPERIENCE MAY NOT APPEAR TO BE DRUG RELATED:

Department of Medical Oncology and Immunology
Hoffmann-La Roche Inc.

Telephone: Monday to Friday, 8:30 am to 5:00 PM (EST)
(201) 235-5850 - Dr. Paul Nadler

Weekends, holidays and nights
(201) 235-2355 (ask for physician on call)

Such preliminary reports will be followed by detailed descriptions later which will include copies of hospital case reports, autopsy reports and other documents when applicable.

I. Procedures for Removing Patients from Study:

Should the subject decide to withdraw, every effort will be made by the investigator to complete and report the observations as thoroughly as possible, including a complete final evaluation at the time of the subject's withdrawal with an explanation of why the subject is withdrawing from the study. A Case Report Form must be completed for any patients who receive any amount of medication coded for this study.

Patients may be removed from the study for any of the following reasons:

1. Categories of Early Termination

- a. Adverse reactions too severe to allow continuation.
- b. Patient desires to withdraw from further participation in the study
- c. An intercurrent illness which would prevent completion of the study.
- d. Failure of the patient to cooperate in the study.
- e. Any other reason which, in the opinion of the investigator, would justify removing the patient from the study. If such is the case, the reasons justifying removal must be recorded in the Case Report Form.

2. Replacements

If a patient withdraws from the study, a replacement subject will be obtained using the original entry criteria.

If the code is broken because of an adverse experience, that patient may not receive any additional test medication.

J. Conditions For Modifying, or Terminating the Study

Modifying -

If preliminary or interim review indicates that modifications should be made in the experimental design, dosages, parameters, patient selection, etc., these changes will be made after appropriate consultation between the sponsor and the investigator and will be accomplished through appropriate amendments to this protocol and approval by the appropriate review committees.

Terminating -

If the sponsor and/or the investigator should discover conditions arising during the study that indicate it should be terminated, an appropriate schedule for termination will be instituted.

III. Analysis of Data

Sample Size

Patients without a positive culture will be excluded from the final analysis of this study and will not be counted towards the final number of evaluable cases in any center. A total of 135 completed cases with HSV-II isolated from genital lesions (45 on each arm) will be required for final analysis. Patients who receive four or more doses of the test medications will be included for efficacy analysis.

The sample size is determined on the basis of:

50% decrease in the mean number of recurrences in the 12 month period following the therapy. Using an estimated range of 0-24 mean recurrences in 12 months with one-sided $\alpha = 0.01$, power = 0.90, a sample size of 38 is required. This calculation has been made by assuming that IV acyclovir alone will not significantly alter the frequency of recurrences after a primary or initial episode of genital herpes.

Efficacy Parameters

All the parameters for patients receiving IM interferon alone, IV acyclovir alone, or both agents will be compared. The number of recurrent episodes observed in patients in the three treatment groups will be compared. Analysis of the results by sex will be performed in order to detect potential differences in therapy in males and females.

We will also compare the following parameters of the primary/initial episode:

- a. the duration of viral shedding
- b. the time to crusting of lesions
- c. the time to healing of all lesions
- d. severity and duration of pain
- e. number of lesions occurring after the onset of therapy
- f. change in diameter of lesions during therapy

Safety Parameter

Adverse experiences will be compared between the groups receiving intravenous acyclovir (Zovirax®), IM rIFN- α A, or both agents.

IV. WARNINGS

SPECIAL PRECAUTIONS REGARDING PROCREATION WHILE ON INJECTABLE INTERFERON STUDIES

Teratology and reproduction studies of rIFN- α A have not yet been completed. In addition, there are no adequate, controlled studies of any interferon in pregnant women. The effect on spermatogenesis is also unknown.

For this reason, women of childbearing potential and fertile men will be excluded unless using effective contraception during the interferon treatment period. Women who are pregnant and lactating women will also be excluded. A pregnancy test will be performed on each female of childbearing potential at entry into the study.

The subject consent form should stress that lack of information regarding potential risk to the fetus conceived while the patient or the sexual partner are in the study.

V. Precautions

Since the safety of the combination has not been established definitively, close attention should be paid to all potential adverse experiences occurring during this study. For information regarding precautions and adverse reactions with these drugs, the investigator is referred to the Investigational Drug Brochure and supplement, copies of which will be supplied by the sponsor and to the Zovirax® package insert.

VI. Institutional Review

It is the understanding of the sponsor that this protocol and any modifications, as well as appropriate subject consent procedures will be reviewed and approved by an Institutional Review Committee. This Committee must operate in accordance with the Federal Regulations published in the Federal Register of January 27, 1981. A letter or certificate of approval will be sent to the sponsor prior to initiation of the study.

VII. Patient Consent

It is the responsibility of the investigator to obtain informed written consent from each subject participating in this study. This consent must be obtained in accordance with Federal Regulations published in the Federal Register on January 27, 1981.

Every effort will be made to maintain the anonymity and confidentiality of medical records during this treatment program. However, because of the experimental nature of this treatment, periodic monitoring of medical records will be made by representatives of Hoffmann-La Roche Inc. (the sponsor) and may be made by the Food and Drug Administration. A statement to this effect should be included in the subject consent form.

The subject consent form should adequately reflect the data provided regarding adverse experiences associated with either rIFN- α A or Zovirax® and the possibility of unexpected toxicity (see Background, IDB and supplements, and Zovirax® package insert). It should stress the lack of information regarding potential risk to the fetus conceived while the patient is on the study.

VIII. Investigator's Responsibilities

- A. Confidentiality - By conducting this study the investigator affirms to Hoffmann-La Roche that he/she will maintain in confidence information furnished to him/her by Hoffmann-La Roche and data generated in this study except as provided below and will divulge such information to his/her review committee under an appropriate understanding of confidentiality with such committee.

It is noted that publication of a summary of the results of this study in the customary manner is permissible in the view of Hoffmann-La Roche and is not inconsistent with the preceding affirmation. Any formal publication of the study will be considered as a joint publication by the investigators and the appropriate personnel of Hoffmann-La Roche. Authorship will be determined by mutual agreement.

For any publications or presentations a manuscript of the paper or abstract will be forwarded to Hoffmann-La Roche before outside submission. The cumulative experience of all participating study centers will be pooled for analysis. The results of any individual center will not be presented or published as an individual study.

- B. Case Report Forms - Individual Case Report Forms must be completed in black ink or typewritten. All data must be carefully completed to permit meaningful interpretation. Case Report Forms are designed for computer processing and analysis.

A Case Report Form is required for each subject who has received or taken any drug prepared for this protocol. A copy of the Case Report Form will be retained in the investigators file for two years after all investigational use of the drug is discontinued and the FDA so notified or until two years after a New Drug Application is approved. Sections of the Case Report Forms are to be promptly completed and returned to the sponsor within 2 weeks of a patient completing each section of the study.

- C. Laboratory Reports - Prior to initiation of the study, the investigator must supply the sponsor with the ranges of laboratory normal values for the laboratory utilized, also noting its certification. Laboratory test results should be entered on the appropriate pages of the Case Report Form. When required by the protocol, additional reports will be attached to the Case Report Form. If unexplained laboratory abnormalities occur, corroborative tests will be done until these have returned to normal and/or adequate explanation of the abnormality is found.

- D. Other Reports - Copies of records pertinent to the study (e.g., laboratory data, X-ray reports, patient charts) must be made available to the sponsor, if requested, with due precaution to confidentiality for the subject.

- E. Monitoring Requirements - The sponsor reserves the right to monitor this study at appropriate times as deemed necessary, by personal visit or telephone.

- F. Drug Dispensing Log - Subjects entered into the test drug trial will be assigned a study number in the chronological order in which they begin drug therapy. A clear record of each dose of drug dispensed must be maintained by the investigator.

- G. Patient Exclusion Record

The patient exclusion record will be completed for any patient who is asked to be in this study or otherwise considered for this study but is excluded for any reason including but not limited to refusal to participate.

APPENDIX A

STUDY FLOW CHART, PROTOCOL #2661A

STUDY PARAMETER	Pre- drug Base- line	DAYS OF STUDY												16, 17 or 18	20, 21 or 22	q.4 days	MONTHS OF FOLLOW-UP	
	1	2	3	4	5	6 or 7	8 or 9	10 or 11	12 or 13								1-11	12
HBsAg*	X																	
PREGNANCY TEST (if applicable)	X																	
INTRAVENOUS ACYCLOVIR (3x/day): OR PLACEBO		TID	TID	TID	TID													
IM INJECTION OF rIFN- α A OR PLACEBO		X	X	X	X	X												
PHYSICAL EXAM AND HISTORY	X														X			X**
VITAL SIGNS	X		X	X	X	X									X			
EXAM OF HERPES GENITALIS	X		X	X	X	X	X	X	X	X°	X°	X°	X°	X°	X°			
HISTORY OF GENITALIS RECURRENCES																	H	H
EXAMINATION FOR TOLERANCE	X		X	X	X	X ^a												
CBC, PLATELETS	X			X		X		X							X			
SMA-12	X			X		X		X							X			
URINALYSIS	X			X		X		X							X			
rIFN- α A ANTIBODY TITER	X														X			
HSV IDENTIFICATION	X ^b																	
VIRAL CULTURE	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X°		
HSV ANTIBODY TITER	X														X			

* To be repeated if patient received a blood product.

** If indicated.

° If lesions persist, perform exam.

°° To be continued every 4 days if lesions persist.

H History taken by post-card or telephone. Patient should be seen at least once during each recurrence.

a To be followed at each visit if necessary.

b Virus identification at baseline or least once during the initial episode.

c Perform baseline and on last positive viral culture.

APPENDIX B

CLINICAL ADVERSE EXPERIENCES

CATEGORIES FOR DETERMINING RELATIONSHIP TO TEST DRUG

REMOTE

In general, this category can be considered applicable to those adverse experiences which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the test drug. An adverse experience may be considered remote if or when, for example:

1. It does not follow a reasonable temporal sequence from administration of the drug.
2. It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
3. It does not follow a known response pattern to the suspected drug.
4. It does not reappear or worsen when the drug is readministered.

POSSIBLE

This category applies to those adverse experiences in which, after careful medical consideration at the time they are evaluated, the connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An adverse experience may be considered possible if or when--

1. It follows a reasonable temporal sequence from administration of the drug.
2. It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
3. It follows a known response pattern to the suspected drug.

APPENDIX B (Continued)

CLINICAL ADVERSE EXPERIENCES

PROBABLE

This category applied to those adverse experiences which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the test drug. An adverse experience may be considered probable if, for example:

1. It follows a reasonable temporal sequence from administration of the drug.
2. It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
3. It disappears or decreases on cessation or reduction in dose.**
4. It follows a known pattern of response to the suspected drug.

**There are important exceptions when an adverse experience does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists; e.g., 1) tardive dyskinesias, 2) fixed drug eruptions.

APPENDIX C

PROCEDURE FOR COLLECTION AND SHIPMENT
OF BLOOD SPECIMENS

Assessment of the presence of serum antibodies to rIFN α A will be performed on all subjects who receive interferon on a research protocol. If samples of blood products are to be shipped to Hoffmann-La Roche Inc. for pharmacokinetic or other studies, each patient involved must be tested for the presence of Hepatitis B surface antigen (HBsAg) before shipment is made. If the results of the HBsAg screening are negative, this will be indicated in the appropriate space on the case report form and the samples may be shipped. If a patient yields a positive test for HBsAg, this must be recorded in the case report form and samples from this patient may not be shipped to Hoffmann-La Roche, Inc. without special permission. The medical monitor must be contacted by the investigator to obtain that special permission each time a sample from a HBsAg-positive patient is to be shipped. This screening for HBsAg must be performed on entry into the study and following the administration of any blood product to the patient.

- A. Collection Schedule: As per protocol and depicted in Flow Sheet in Appendix A.
- B. Collection, Labeling and Storage:
 - 1. Blood - for interferon antibodies.
 - a. Three (3) ml of blood will be drawn in a sterile syringe or directly into a glass vacutainer with a red stopper.
 - b. If drawn into a syringe the blood will be immediately transferred to a glass centrifuge tube and allowed to clot at room temperature.
 - c. Refrigerate clotted sample for 30 minutes at 4°C in an upright position to contract the clot.
 - d. Centrifuge at 4° for 10 min at 1000 r.p.m. to extract additional serum.
 - e. Pippette all serum into a 2 ml screw cap vial of the Nunc type (to be supplied by sponsor.)

It is imperative that serum and not plasma be sent!

APPENDIX C (continued)

- f. Label the Nunc tubes with the cryogenic marker provided and immediately freeze at -70°C . Labeled samples should bear the following information:

Protocol No.: 2661 IF antibodies
Patient's initials and identification number:
Date and Code:
Hour sample was drawn [e.g. 0 hours (baseline)]

2. Storage

- a. All serum samples should be stored at -70° until time of shipment.

3. Shipment

- a. Samples for each week should be accumulated and shipped in monthly or appropriate intervals on Monday.
- b. The approximately 2 ml serum samples for interferon antibodies in the 2 ml Nunc tubes should be placed in the plastic zip-lock bags provided and logged on the accompanying Clinical Biochemistry Request forms for Interferon antibodies.
- c. The plastic zip-lock bags will be placed in an insulated mailer (provided) with sufficient dry ice to last 72 hours. Fill any space in mailer with packing material to prevent tumbling of contents.
- d. Address container to:

Dr. H. Spiegel
Dept. of Clinical Laboratory Research
Bldg. 34, Room 524
Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Label return address on container!

Write boldly on all six sides: RUSH - HUMAN BLOOD
DRY ICE

- e. Shipment must be made by Federal Express.
The bill number must be transmitted to Dr. Spiegel by phone before shipment of the test specimens.

Dr. Spiegel may be reached at Roche at (201) 235-5124.
In Dr. Spiegel's absence, Dr. Paul Nadler should be notified at (201) 235-5850.

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