Safety and Tolerance of Recombinant Interferon Alfa-2a (Roferon®-A) in Cancer Patients

GARY J. JONES, MS, AND LORETTA M. ITRI, MD

Recombinant interferon alfa-2a (Roferon®-A, Hoffmann-La Roche Inc., Nutley, NJ) has been evaluated in clinical trials of more than 1300 patients with a broad spectrum of oncologic disease. Patients with either solid tumors or hematologic malignancies were treated with daily or three-times-weekly intramuscular injections for induction periods ranging from 8 to 16 weeks. Doses ranged from 1×10^6 units to 124×10^6 units per injection. When administered in low daily doses (approximately 3×10^6 units), Roferon®-A was well tolerated, and dose attenuation was rarely required. Change to a three-times-weekly treatment regimen at the same dose was usually sufficient to control toxicity when it occurred in this group of low-dose patients. Those patients receiving higher doses frequently required dose attenuation to 50% of the starting dose to improve clinical tolerance. Virtually all patients treated with Roferon®-A experienced some degree of acute toxicity manifested as fever, chills, myalgia, and/or headache. These reactions usually occurred with initial dosing and frequently improved spontaneously with continued administration of the drug. Acetaminophen pretreatment was generally useful in ameliorating these symptoms. Common adverse experiences occurring after repeated dosing included fatigue, anorexia, and weight loss. Serious adverse reactions including cardiovascular and neurologic toxicity have occurred infrequently, primarily at higher doses. Hematologic toxicity and elevations in liver function parameters were also observed, but rarely required dose attenuation. Adverse effects were usually reversible after dose reduction or discontinuation of therapy. Approximately 27% of all patients developed antibodies to rHuIFN-α2A during treatment. No adverse clinical sequelae have been associated with antibody development to date.

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INTERFERONS are proteins produced by cells in response to a variety of stimuli including viruses, bacteria, double-stranded RNA, mitogens and antigens.[1,2] The interferons have been demonstrated to exhibit a number of antiviral, antiproliferative, and immunomodulatory properties.[3]

Three major, antigenically distinct classes of interferons have been identified. Generally, alpha (α) and beta (β) interferons are produced by stimulated leukocytes and fibroblasts, respectively; both types are acid stable. Gamma (γ), or immune, interferon is synthesized by T-lymphocytes in response to antigens and mitogens and is acid labile. To date, multiple distinct alpha interferon species[4] have been isolated, whereas only one beta[5] and one gamma[6] species have been identified.

The antiproliferative mechanisms of action of the interferons have proven difficult to elucidate, as reported in a number of extensive reviews.[7,8] A myriad of hypotheses about mechanisms of action exist. These include depression of DNA and/or protein synthesis, alterations in cellular morphology, modulation of membrane antigen expression, modulation of cellular differentiation, enhancement of antibody formation, stimulation of natural killer (NK) cells and macrophages, prolongation, inhibition, and interruptions of the cell cycle, and increased T-cell cytotoxicity.

In the earliest clinical trials,[9–11] small quantities of alpha interferon were obtained through viral induction of human peripheral blood leukocytes resulting in a product of only 0.1% to 1.0% purity. The scarcity of interferon restricted the number of patients who could be treated and permitted clinical investigations of only a limited dose range. It was impossible to determine whether the adverse effects experienced by recipients of these crude interferon preparations were due to the impurities present in the preparation or to the interferon itself.

In 1980, the gene for mature human alpha-A interferon was successfully cloned, engineered, and expressed in *Escherichia coli* using recombinant technology. This resulted in the production of large quantities of highly purified, bacterially synthesized human alpha-A[12] interferon,

From the Department of Clinical Oncology, Clinical Research and Development, Hoffmann-La Roche Inc., Nutley, New Jersey.

Address for reprints: Loretta M. Itri, MD, Hoffmann-La Roche Inc., Building 115/5, 340 Kingsland Street, Nutley, NJ 07110.

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TABLE 1. Diagnosis of 1019 Patients Treated with Roferon®-A

Diagnosis	No. of Patients
Solid tumors	
Genitourinary tumors	311
Malignant melanoma	201
Soft tissue sarcomas	165
Breast cancer	46
Lung cancer	46
Gastrointestinal cancers	24
Sarcomas of bone	18
Carcinoma (site unspecified)	3
Brain tumors	1
Liver tumors	1
Subtotal	816
Hematologic malignancies	
Leukemias	99
Non-Hodgkin's lymphomas	87
Plasma cell neoplasms	16
Hodgkin's disease	1
Subtotal	203
Total	1019

now designated interferon alfa-2a (rHuIFN-α2A; Roferon®-A, Hoffmann-La Roche Inc., Nutley, NJ). Roferon®-A is a single species of human interferon purified to approximately 96% homogeneity with a specific activity of 2×10^8 units/mg protein. The molecule consists of 165 amino acids and has a molecular weight of 20,000 daltons.

Clinical trials with Roferon®-A were initiated in January 1981. Since that time, approximately 1300 patients, exhibiting a broad spectrum of oncologic disease, have received treatment under experimental protocols. This paper presents the cumulative safety and tolerance data obtained from patients who received Roferon®-A by intramuscular administration while participating in Phase II and III clinical trials. Phase I patients have not been included in this analysis because varied doses and schedules were investigated during this phase of development.[13-17]

The overall incidence of clinical adverse effects and laboratory abnormalities in this patient population is presented here. An analysis of the distribution of adverse effects in patients with solid tumors *versus* those with hematologic malignancies is also discussed. The relationship of incidence of clinical adverse effects to average dose per injection is also presented.

Patients and Methods

During Phase II and III clinical trials, 1019 patients (678 male, 341 female), diagnosed as having a variety of malignancies (Table 1), were treated with daily or three-times-weekly intramuscular injections of Roferon®-A. The age of this patient population ranged from 13 to 83 years, and the median age was 53 years. A small number of patients received Roferon®-A by subcutaneous (8), intraperitoneal (6), and intravenous (13) routes of administration, but these groups are not included in this discussion because of their small numbers. Some of the data contained in this report have not been published and represent the cumulative toxicity data reported to Hoffmann-LaRoche as the IND sponsor for Roferon®-A clinical studies.

Because of the diversity of the patient population and the indications studied, patient entry and exclusion criteria varied to a small degree in different studies, but, overall, the criteria remained consistent throughout. In general, patients were eligible for entry into Roferon®-A clinical trials if they were at least 18 years of age, had histopathologically documented disease with a prognosis for life expectancy greater than the duration of induction, had a performance status of greater than or equal to 60 (Karnofsky scale) or less than or equal to 2 (Eastern Cooperative Oncology Group scale), and required no palliative treatment during the study. Written informed consent was obtained from all patients.

Those excluded from entry into the studies were pregnant and lactating women, fertile men and women not using effective contraception, patients having had surgery within four weeks of entry into the study (unless fully recovered), and patients with a history of previous malignancy (excluding noninvasive cutaneous carcinoma). Other clinical criteria for exclusion included cardiac disease or any history of cardiac disease, central nervous system metastases or seizure disorders, or severe intercurrent infection. Impaired renal, hepatic, and/or hematologic functions (serum creatinine level >1.8–2.0 mg/dl; total bilirubin value >1.4 mg/dl; leukocyte count $\leq 3{,}000/mm^3$; granulocyte count $\leq 1{,}000/mm^3$; platelet count $\leq 100{,}000/mm^3$; and serum calcium level >12 mg/dl) were the laboratory criteria for exclusion. Chemotherapy or immunotherapy for the primary diagnosis received within four weeks of study entry were also criteria for exclusion.

Induction therapy consisted of daily dosing, three-times-weekly dosing, or daily escalating dose injections (Table 2).[18-35] In the last-named dosing group, the dose was increased over 12 days from 3×10^6 units to 36×10^6 units. Therapy was continued at the highest dose for the remainder of treatment in the absence of toxicity. Depending on the study, induction duration ranged from eight to 16 weeks. Responding patients and, in some cases, those whose disease remained stable during induction therapy were allowed to continue treatment on a three-times-weekly maintenance schedule until their disease progressed or until they were removed from study.

Starting doses ranged from 1×10^6 units to 124×10^6 units per injection. Dose attenuation was permitted, based on toxicity (Table 3), according to the following guidelines:

1. For 1+ toxicity, Roferon®-A administration continued.
2. For 2+ or 3+ toxicity (other than that of a neurologic origin), Roferon®-A was discontinued until a return to 1+ toxicity or baseline condition was achieved, and then therapy was resumed at 50% of the dose at which toxicity occurred. If 2+ or 3+ toxicity recurred at the 50% dose, administration was again discontinued until a return to 1+ toxicity or baseline condition was achieved and therapy was then resumed at 10% of the dose at which attenuation originally began. The drug was discontinued if 2+ or 3+ toxicity recurred at the 10% dose.
3. For 3+ neurologic toxicity, the patient was withdrawn from the study.

For those reactions not defined in the toxicity table, the following guidelines were used:

1. Mild (1+): Awareness of sign or symptom, but easily tolerated.
2. Moderate (2+): Discomfort great enough to cause interference with usual activity.
3. Severe (3+): Incapacitating symptoms causing inability to work or to perform usual activities.

Patient safety was monitored through clinical and laboratory examinations. A history, physical examination including weight and performance status assessment, neurologic exam, hematology profile, SMA-12, routine urinalysis, electrocardiogram (ECG), and chest x-ray were obtained for each patient before treatment initiation. The

TABLE 2. Starting Doses and Schedules for Administration of Roferon®-A

Diagnosis	Dose and schedule
Heterogenous cancers sensitive *in vitro* in tumor stem cell assay	86×10^6 U, tiw
Non-Hodgkin's lymphoma[18]	$12{,}50 \times 10^6$ U/m², tiw
Chronic lymphocytic leukemia[19,20]	$12{,}20 \times 10^6$ U/m², tiw
Mycosis fungoides[21]	3×10^6 U, qd 3 to 36×10^6 U, qd* 50×10^6 U/m², tiw
Breast cancer[22,23]	$9{,}50 \times 10^6$ U/m², tiw 20×10^6 U/m², qd
Colon cancer[24]	50×10^6 U/m², tiw
Small cell[25] and non-small cell[26] lung cancer	2×10^6 U/m², qd $20{,}50 \times 10^6$ U/m², tiw
Multiple myeloma	12×10^6 U/m², qd
Ovarian cancer[27]	20×10^6 U/m², tiw
Cervix cancer	50×10^6 U/m², tiw
Osteogenic sarcoma	50×10^6 U/m², tiw
Malignant melanoma[28–30]	3 to 36×10^6 U, qd $12{,}50 \times 10^6$ U/m², tiw 50×10^6 U/m², tiw
Renal cell cancer[31–32]	$2{,}20 \times 10^6$ U/m², qd 3 to 36×10^6 U, qd 50×10^6 U/m², tiw
Kaposi's sarcoma[33]	3 to 36×10^6 U, qd $20{,}36 \times 10^6$ U, qd
Hairy cell leukmeia[34,35]	$3, 12 \times 10^6$ U, qd

* Dose was escalated from 3×10^6 units to 9×10^6 units to 18×10^6 units over 9 days to continue at 36×10^6 units if tolerated.
tiw: three times weekly; qd: daily.

TABLE 3. Criteria for Grading Adverse Experiences during Roferon®-A Treatment

	1+ toxicity (mild) (objectively present but not disabling)	2+ toxicity (moderate) (disabling, but hospitalization not necessary)	3+ toxicity (severe) (disabling, may require hospitalization)
Hematologic	WBC, 3000–2000; granulocytes, 1000–750; or platelets, 100,000–75,000	WBC, 1999–1000; granulocytes, 749–500; or platelets 74,999–50,000	WBC <1000; granulocytes <500, or platelets <50,000
Nausea/vomiting	Nausea with 0 to 4 episodes of vomiting/day	5 to 10 episodes of vomiting/day	Vomiting >10 ×/day; IV fluids required
Diarrhea	1 to 4 abnormal bowel movements/day	5 to 10 abnormal bowel movements/day	>10 abnormal bowel movements/day
Hepatic	Increase in hepatic enzymes or bilirubin to <1.5 × upper limits of normal	Increase in hepatic enzymes or bilirubin to 1.5 to 3.0 × upper limits of normal	Increase in hepatic enzymes or billirubin to >3 × upper limits of normal or prolongation of prothrombin time to >1.5 × control
Renal	Increase of serum creatinine to <1.5 × upper limits of normal	Increase of serum creatinine to 1.5 to 3.0 × upper limits of normal	Increase of serum creatinine to >3.0 × upper limits of normal
Neurologic	Mild lethargy, paresthesias, or hyporeflexia	Transient mild confusion, gait disturbance, or objective weakness	Severe confusion, obtundation, coma, or seizures
Anorexia and weight loss	Anorexia; <5% weight loss	Anorexia; 5% to 10% weight loss	Anorexia; >10% weight loss
Fatigue	In bed <50% of the time	In bed >50% of the time	Unable to care for self

WBC: leukocyte count; IV: intravenous

physical examination and urinalysis were repeated approximately every 4 weeks, and the hematology and blood chemistry testing were conducted every 1 to 2 weeks throughout the duration of the induction phase. All examinations were required every 4 weeks during maintenance therapy. ECG and chest x-rays, as well as any other testing deemed necessary by the investigator, were repeated as clinically warranted.

Serum for the determination of antibodies to rHuIFN-α2A was obtained for each patient before the first injection and at the end of both the induction and maintenance periods ($\geq$48 hours after the last injection); rHuIFN-α2A antibody levels were measured by both virus neutralization bioassay[36] and enzyme immunoassay.

The incidence of clinical adverse effects and laboratory abnormalities was evaluated separately for patients with solid tumors and for those with hematologic malignancies. Calculation of the percentage of incidence was based on the total number of patients treated in all studies. The relationship of dose to the development of toxicity was also examined.

Analysis of the relationship of toxicity to average dose per injection was determined. The average daily dose per injection was calculated by dividing the total cumulative dose at the time of onset of the adverse event by the total number of injections received until that time. For the purposes of analysis, the following dose categories were defined: 0 to 3×10^6 units, $>3 \times 10^6$ units to 18×10^6 units, $>18 \times 10^6$ units to 36×10^6 units, $>36 \times 10^6$ units to $<72 \times 10^6$ units, and $\geq 72 \times 10^6$ units. Calculation of percentage of incidence was based on the total number of patients receiving a dose within each respective dose category. Patients were considered evaluable for safety analysis if they had received one dose of Roferon®-A.

Results

Virtually all of the 1019 patients who received Roferon®-A experienced an adverse effect during treatment. The adverse effects were usually mild and reversible, but were occasionally of a serious nature. The adverse events observed during Roferon®-A treatment can most easily be classified as either acute or of later onset. Acute effects (occurring within the first 72 hours of treatment) included the flu-like symptoms of fever (86%), chills (62%), myalgias (57%), headache (46%), arthralgia (12%), and diaphoresis (8%). In the majority of patients, these symptoms usually occurred within a few hours of drug administration and could often be ameliorated by pretreatment with acetaminophen. Tolerance usually developed to acute adverse effects within the first few weeks of therapy, regardless of dose or schedule.

Fatigue (90%), the most frequently encountered adverse experience, and anorexia (68%) were the most important adverse reactions occurring after repeated administration of drug, and were often dose limiting. The onset of these symptoms usually occurred during the first 1 to 2 weeks of treatment, and symptoms generally persisted for the duration of therapy with resolution on discontinuation of treatment. Frequently observed gastrointestinal symptoms included nausea (53%), emesis (30%), and diarrhea (34%), which were usually mild in nature. Central nervous system toxicity was most commonly manifested as vertigo (19%), decreased mental status (12%), confusion (10%), and depression (6.5%). These symptoms, the majority of which were mild, generally resolved on discontinuation of the drug. Coma occurred in six patients, all of whom had widespread metastatic cancer. One cerebrovascular accident occurred in a patient with a history of hypertension. Six cases of encephalopathy, two cases of transient ischemic attack, and five seizures occurred in patients during treatment. The main peripheral nervous system adverse effects observed were mild paresthesias (7%) and numbness (4%).

Cardiovascular toxicity was experienced by approximately 15% of patients. Hypotension (6%), which was usually mild, was the most frequently reported adverse experience. Chest pain of uncertain etiology was reported in 3% of patients. Five patients (less than 1%) experienced myocardial infarctions: two of these patients had a prior history of ischemic heart disease, and one of these had previously received Adriamycin (doxorubicin). One patient had a prior history of atypical angina, one was hypertensive, and the remaining patient had no history of preexisting disease. The acute flu-like symptoms associated with initial Roferon®-A administration may have exacerbated preexisting heart disease in some of these patients. Later studies specifically excluded patients with any known prior cardiac disease. The relationship of these adverse effects to prior treatment with cardiotoxic chemotherapy is currently unknown.

Integumentary adverse effects included alopecia of varying degree (10%), rash (7%), and exacerbation of herpes labialis (5%). The most frequently observed miscellaneous adverse effects were dysgeusia (14%), weight loss (13%, 3.0% lost >10% total body weight), cough (10%), dyspnea (7.5%), and dry pharynx (5%). Other clinical adverse effects have been infrequently reported,[37] but are beyond the scope of this report.

Analysis of the relationship of incidence of adverse effects to the average dose per injection indicates a possible trend toward increased frequency of certain central nervous system, cardiovascular, gastrointestinal, and peripheral nervous system adverse reactions (Table 4) with higher doses. Possible dose-related effects include lethargy, hypotension, arrhythmias, nausea, emesis, anorexia, and paresthesias. Incidence of confusion and myalgias also appears to increase with increasing dose when incidence

is calculated in relation to average dose per injection. The incidence of clinical adverse effects in patients with either hematologic malignancies or solid tumors is generally similar.

When administered in low daily doses (approximately 3×10^6 units), Roferon®-A was well tolerated, and dose attenuation was rarely required. Change to a three-times-weekly treatment regimen at the same dose was usually sufficient to control toxicity when it occurred in this group of patients. Patients receiving higher doses frequently required dose attenuation to improve tolerance.

The most frequent laboratory abnormalities were decreases in hematologic parameters and increases in liver function tests, which were rarely severe or dose limiting. Hematologic toxicities were primarily leukopenia (69%), decreases in hematocrit (69%) and hemoglobin (65%) levels, neutropenia (58%), and thrombocytopenia (42%).

The most common hepatic toxicities were elevated levels of serum glutamic oxaloacetic transaminase (77%), alkaline phosphatase (48%), lactic dehydrogenase (47%), and bilirubin (31%); these conditions generally did not require dose attenuation.

Mild proteinuria (25%), increased leukocyte (14%) and erythrocyte counts (4.5%) in the urinary sediment, and elevated levels of blood urea nitrogen (10%), serum creatinine (10%), and uric acid (15%) constituted the majority of renal and urinary toxicities. One occurrence of reversible nephrotic syndrome[38] and four episodes of renal failure, two of which were reversible on drug discontinuation, have been reported.

A comparison of the incidence of laboratory abnormality by tumor type (solid *versus* hematologic) showed little difference between the two groups, with a few exceptions. Thrombocytopenia, leukocytosis, and lymphocytosis appeared with increased frequency in patients with hematologic malignancies, an event that is probably due to the nature of the underlying disease in these patients.

Of a total of 559 evaluable patients surveyed, 153 (27.4%) were determined to have developed neutralizing antibodies against rHuIFN-α2A during the course of treatment. Of these patients, 38 also developed neutralizing antibodies to human alpha interferon. Patients were considered evaluable if they tested negative for the rHuIFN-α2A antibody before treatment and were tested for the antibody while on therapy with Roferon®-A or at completion of therapy. Antibodies were detected, prior to initial treatment, in four out of 749 patients for whom adequate baseline serum samples were available. No follow-up serum specimens were available for three of these patients, and one patient showed an increase in antibody titer during treatment. Table 5 presents data on antibody development in relation to diagnosis. Of particular interest is the incidence of antibody development in patients with renal cell carcinoma and Kaposi's sarcoma. To date, no deleterious clinical or laboratory effects have been associated with the development of neutralizing antibodies to rHuIFN-α2A.

TABLE 4. Percentage of Incidence of Adverse Experiences as a Function of Average Dose per Injection

	Percentage of incidence				
	Dose category				
Adverse experience	0–3 $\times 10^6$ U	>3–18 $\times 10^6$ U	>18–36 $\times 10^6$ U	>36–<72 $\times 10^6$ U	≥72 $\times 10^6$ U
Lethargy	0.0	0.7	1.6	3.7	4.8
Confusion	0.8	3.8	9.7	5.2	9.3
Hypotension	0.3	0.0	1.6	6.7	9.6
Arrhythmia	0.3	0.2	1.0	0.7	2.7
Nausea	19.0	31.5	32.0	28.7	52.1
Emesis	7.4	13.9	18.5	18.3	33.1
Anorexia	21.8	42.1	43.6	48.1	66.3
Paresthesia	1.5	1.7	5.1	4.1	7.2
Myalgia	35.0	31.3	35.5	28.7	53.0

Discussion

Treatment of a variety of human malignant disorders with interferon alfa-2a has shown promising results. Earlier clinical studies performed with nonrecombinant interferons suggested that the observed toxicities might be due to impurities in these preparations.[9–11] The results presented here provide evidence that highly purified recombinant interferon alfa-2a is responsible for many of the adverse events originally attributed to contaminants.

Although many dosing schedules and ranges have been evaluated, the profile of clinical and laboratory adverse experiences of this drug has remained remarkably constant. With initial dosing, a flu-like syndrome of varying degree is almost universally observed; this syndrome can be ameloriated in most cases with acetaminophen pre-

TABLE 5. Antibody Development to rHuIFN-α2A in 559 Patients

	Antibody-positive patients	
Diagnosis	%*	(N)†
Renal cell carcinoma	45.9	(185)
Kaposi's sarcoma	36.6	(60)
Sarcoma (other)	28.6	(14)
Lymphomas	21.7	(60)
Lung cancer	21.4	(14)
Malignant melanoma	16.7	(108)
Plasma cell neoplasma	16.7	(12)
Gastrointestinal cancers	14.3	(14)
Breast cancer	5.9	(17)
Leukemias	4.6	(65)
Other	0.0	(10)

* Percentage of incidence by diagnosis.
† Number of evaluable patients by diagnosis.

treatment. These effects are usually self-limiting and generally resolve after several doses have been administered. While the acute effects are generally not of serious clinical concern, special caution should be exercised in the treatment of patients with known or suspected cardiac disease in whom the stress associated with fever may exacerbate otherwise quiescent disease. Each case of this type should be carefully assessed and interferon alfa-2a should be administered only if expected clinical benefit outweighs the associated risks.

With repeated dosing, fatigue and anorexia, with attendant weight loss of varying degree, have been observed in the majority of patients. Because of the nature of the underlying disease in patients receiving interferon alfa-2a treatment, it was frequently difficult to ascertain whether these effects were solely related to the drug or were, to some degree, a manifestation of the malignant disease.

The most serious adverse effects associated with interferon alfa-2a treatment are those related to the central nervous and cardiovascular systems. Dizziness, lethargy, mild confusional state, and depression generally resolved with discontinuation of the drug. However, on rare occasion, patients developed severe and occasionally irreversible events including seizures, transient ischemic attacks, stroke, encephalopathy, and coma. It is, therefore, advised that patients with known seizure disorders or brain metastases be treated with interferon alfa-2a only if the risks to the patient are acceptable when compared with the possible clinical benefits.

Primary laboratory abnormalities observed during interferon alfa-2a treatment are decreases in hematologic parameters and elevations of liver function tests. These abnormalities have only rarely been of clinical significance and are of most concern in patients with cytopenias or liver dysfunction prior to treatment onset. The development of antibodies to interferon alfa-2a has been observed in approximately one quarter of the evaluable patients but has not been associated with clinical sequelae to date.

Many other adverse events have been reported during the conduct of the studies[18–35] included in this summary, and a few have been the subject of published reports.[39–41] As with most new therapies evaluated for the management of cancer patients, it is frequently difficult to assign causality to the agent under evaluation. Administration of interferon alfa-2a is clearly associated with a specific pattern of adverse experiences that can be managed in most cases by adjustments in dose to individual patient tolerance. In those patients for whom dose adjustment has not been successful in ameliorating toxicity, discontinuation of the drug has been associated with complete resolution of adverse effects in all but a few cases.

It is apparent that as experience with the administration of Roferon®-A and of other products in this new class of therapeutic agents increases, changes in dosing techniques will result in improved patient tolerance. An example of this is the excellent tolerance of patients with hairy cell leukemia receiving low-dose Roferon®-A (3×10^6 units) in ongoing trials.[34,35] It also appears that patients receiving therapy on the escalating dose schedule may develop an earlier tachphylaxis to the acute adverse experiences. Further, evening administration of Roferon®-A is reported to result in improved tolerance of the drug, permitting patients to lead a more normal lifestyle.[42] The unique toxicity profile of this compound may permit novel approaches to combination with other therapeutic modalities. Studies of this nature are currently under way to evaluate and define the role of this biologic agent in the treatment of many neoplastic diseases.[43]

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