

Interferon Alfacon-1 Plus Corticosteroids in Severe Acute Respiratory Syndrome

A Preliminary Study

Mona R. Loutfy, MD, MPH

Lawrence M. Blatt, PhD

Katharine A. Siminovitch, MD

Sarah Ward, BSc

Bryan Wolff, MD

Hyoung Lho, MD

Dieu H. Pham, MD

Hassan Deif, MD

Elizabeth A. LaMere, MD

Margaret Chang, MD

Kevin C. Kain, MD

Gabriella A. Farcas, BSc

Patti Ferguson, BScPhm

Mary Latchford, BSc, MLT

Gary Levy, MD

James W. Dennis, PhD

Enoch K. Y. Lai, MD

Eleanor N. Fish, PhD

SEVERE ACUTE RESPIRATORY SYNDROME (SARS) is a new infectious disease, probable cases of which are defined by the Centers for Disease Control and Prevention and World Health Organization criteria of fever (temperature $>38^{\circ}\text{C}$), lower respiratory tract symptoms, abnormal chest radiograph results, and laboratory evidence of the Urbani strain of SARS-associated coronavirus infection (SARS-CoV).^{1,2} As of September 26, 2003, the World Health Organization

See also pp 3215, 3229, and 3251.

Context Severe acute respiratory syndrome (SARS) is a new clinical entity for which no effective therapeutic strategy has been developed.

Objective To provide preliminary results on the potential therapeutic benefit and tolerability of interferon alfacon-1 plus corticosteroids for SARS.

Design, Setting, and Patients Open-label study of 22 patients diagnosed as having probable SARS at North York General Hospital, Toronto, Ontario, between April 11 and May 30, 2003.

Interventions Thirteen patients were treated with corticosteroids alone and 9 patients were treated with corticosteroids plus subcutaneous interferon alfacon-1.

Main Outcome Measures Clinical parameters, including oxygen saturation and requirement, laboratory measures, and serial chest radiography results.

Results Resolution of fever and lymphopenia were similar between the 2 treatment groups. Of the 13 patients treated with corticosteroids alone, 5 (38.5%) were transferred to the intensive care unit, 3 (23.1%) required intubation and mechanical ventilation, and 1 (7.7%) died. Of the 9 patients in the interferon alfacon-1 treatment group, 3 (33.3%) were transferred to the intensive care unit, 1 (11.1%) required intubation and mechanical ventilation, and none died. The interferon alfacon-1 treatment group had a shorter time to 50% resolution of lung radiographic abnormalities (median time, 4 days vs 9 days; $P=.001$), had better oxygen saturation ($P=.02$), resolved their need for supplemental oxygen more rapidly (median, 10 days vs 16 days; $P=.02$), had less of an increase in creatine kinase levels ($P=.03$), and showed a trend toward more rapid resolution of lactate dehydrogenase levels compared with the group receiving corticosteroids alone.

Conclusions In this preliminary, uncontrolled study of patients with SARS, use of interferon alfacon-1 plus corticosteroids was associated with reduced disease-associated impaired oxygen saturation, more rapid resolution of radiographic lung abnormalities, and lower levels of creatine kinase. These findings suggest that further investigation may be warranted to determine the role of interferon alfacon-1 as a therapeutic agent for the treatment of SARS.

JAMA. 2003;290:3222-3228

www.jama.com

had recorded a cumulative number of 8098 SARS cases and 774 SARS-related deaths from 27 countries.³ Treatment strategies have included empirical antibiotic therapy, intravenous and oral ribavirin, corticosteroids, and intravenous immunoglobulin.⁴⁻⁶ However, no compelling evidence exists that these strategies improve clinical outcome, and

Author Affiliations: North York General Hospital (Drs Loutfy, Wolff, Lho, Pham, Deif, LaMere, Chang, and Lai and Mss Ferguson and Latchford), Toronto General Research Institute and University of Toronto (Drs Siminovitch, Kain, Levy, and Fish and Mss Ward and Farcas), and Mt Sinai Hospital and University of Toronto (Dr Dennis), Toronto, Ontario; and Intermune Corp, Brisbane, Calif (Dr Blatt).

Corresponding Author and Reprints: Eleanor N. Fish, PhD, Division of Cell and Molecular Biology, Toronto General Research Institute, Canadian Blood Services Bldg, Room 424, 67 College St, Toronto, Ontario, Canada M5G 2M1 (e-mail: en.fish@utoronto.ca).

use of ribavirin has been associated with significant toxic effects.⁶

Hyperimmunoglobulin, protease inhibitors, fusion inhibitors, and interferons represent other therapeutic options for treating SARS patients.⁷ Among these possibilities, interferon alfa is a potential candidate agent and has been recognized to play critical roles in host resistance to viral infection.⁸⁻¹¹ Interferons inhibit viral infection by inducing both innate and adaptive immune responses (eg, by altering the intracellular environment to restrict viral replication, and inducing signaling events that activate immune cell populations and thereby elicit an antiviral immune response).

Interferon alphas have been shown to be of value in the treatment of hepatitis B and C^{12,13} and to induce inhibition of respiratory coronavirus infections, albeit unrelated to the Urbani strain of SARS-CoV.¹⁴⁻¹⁷ In *in vitro* experiments, interferons were effective in inhibiting SARS-CoV,¹⁸ with interferon alfacon-1 exhibiting the highest antiviral activity compared with interferon gamma (Jason Paragas, PhD, US Army Medical Research Institute of Infectious Diseases, unpublished data, May 2003). Interferon alfacon-1 (Infergen, Intermune Corp, Brisbane, Calif) is a synthetic interferon alfa designed to represent a consensus interferon alfa¹⁹ that has been shown in both cell culture systems²⁰ and comparative clinical trials²¹ to inhibit viral replication more potently than other type I interferons.

This preliminary pilot study was initiated to evaluate the potential clinical benefit and safety of interferon alfacon-1 in SARS treatment.

METHODS

Patient Selection

The study population involved 22 patients who were admitted to North York General Hospital (NYGH), Toronto, Ontario, between April 11 and May 30, 2003, and met the Centers for Disease Control and Prevention and World Health Organization criteria for probable SARS.^{1,2} Inclusion criteria for interferon alfacon-1 therapy were

(1) symptom onset within 10 days of the Health Canada approval date (May 29, 2003) for use of interferon alfacon-1 in SARS patients; (2) progressive radiological deterioration over the preceding 48 hours, with greater than 20% involvement of lung fields; (3) progressive deterioration of clinical respiratory status over the preceding 48 hours (decreasing oxygen saturation, increasing respiratory rate, or worsening dyspnea); and (4) patient informed consent for use of interferon alfacon-1. Exclusion criteria included (1) symptom onset more than 10 days before the Health Canada approval date; (2) mechanically assisted ventilation in the intensive care unit (ICU); and (3) contraindication to use of interferon alfacon-1. Nine patients met the inclusion criteria for interferon alfacon-1 treatment.

Patients with probable SARS who were admitted to NYGH during the same period and were administered corticosteroids but not ribavirin served as a comparison group. After May 29, interferon alfacon-1 was offered to all patients who met inclusion criteria. Eleven patients who were admitted prior to May 30 and 2 who declined interferon alfacon-1 treatment comprise the comparison group. All patients admitted prior to April 11, 2003, were excluded because they were included in a previously published study and received ribavirin.⁶

Treatment Protocols

Oral prednisone, 50 mg twice per day, or intravenous methylprednisolone, 40 mg every 12 hours, was administered to all patients who had abnormal chest radiographs. After May 26, 2003, patients exhibiting progressive disease, as characterized by worsening chest radiographs, decreasing oxygen saturation, and worsening dyspnea, received pulsed high-dose intravenous methylprednisolone, 500 mg once per day, for 3 days, followed by a taper and a step down to oral prednisone to complete a 20-day course similar to the previously described protocol.⁵ Patients who required at least 6 L/min of oxygen via nasal prongs to maintain oxygen saturation of at least 92% were transferred to the ICU.

Following Health Canada approval for interferon alfacon-1 use in SARS treatment (May 29, 2003), interferon alfacon-1 was offered through a special access program to all patients who met inclusion criteria for interferon alfacon-1 treatment. Because this study represented the first use of interferon for SARS treatment, the Health Canada provisions for its use in these patients included consultation with an immunologist and submission of a report of adverse events. Institutional research ethics boards for NYGH and the University Health Network reviewed and approved the study protocol and written informed consent was obtained from all participants who received interferon alfacon-1.

Patients were administered subcutaneous interferon alfacon-1 for a total of 10 days, beginning with 9 µg/d for a minimum of 2 days and increased to 15 µg/d if no clinical response was observed. Of the 9 patients treated with interferon alfacon-1, 7 received only the 9-µg dose and 2 received the 15-µg doses. Because of concerns about possible viral and disease rebound if interferon alfacon-1 treatment was stopped before cessation of corticosteroids, a more rapid steroid taper was introduced and interferon alfacon-1 treatment was continued for 1 day after corticosteroid termination. Because of the variable stages of steroid tapering, the interferon alfacon-1 treatment courses ranged from 8 to 13 days. Patients were not discharged to home while still receiving interferon alfacon-1. Patients in the comparison group received corticosteroids but not ribavirin while at NYGH. These patients were chosen prior to data analysis. In both groups, supplemental oxygen therapy was withdrawn when oxygen saturation increased to at least 99% with 1 L/min of oxygen via nasal prongs and at the discretion of treating physicians.

Laboratory Studies and Chest Radiographs

Laboratory investigations included serial hematological and biochemical assays. Acute and convalescent serum

samples were tested for SARS-CoV-associated IgG, using both an enzyme-linked immunosorbent assay and an indirect immunofluorescent assay targeted to the SARS-CoV propagated in Vero E6 cells (National Reference Laboratory, Winnipeg, Manitoba). Serial chest radiographs were obtained from a total of 31 patients at NYGH, including the 22 study patients and 9 additional radiological controls. Radiological controls were randomly chosen from a list of patients investigated for but found not to have SARS and were included to ensure blinding to the disease and the treatment (results of these radiological controls are not included in the data analysis).

Each radiograph was obtained in the frontal projection and was retrospectively reviewed independently by 3 radiologists who were blinded to the identity, diagnosis, and treatment protocol of each patient. For each radiograph, description and an approximate size estimation of the abnormalities, based on percentage of lung involvement, were recorded. For quantitative assessment of radiographic disease progression, the mean percentage of lung involvement reported by the 3 readers was calculated for each radiograph. The radiographic end point used for the analysis was decided prior to any data analysis and was defined as the time from maximum to 50% improved chest radiographic abnormalities. Complete resolution of abnormalities was not considered a practical end point because most patients (18/22) had some residual radiographic findings on the last radiograph, and some did not achieve complete resolution even when followed up beyond the study time frame, up to several months.

Statistical Analysis

Baseline characteristics and treatment of the 2 groups are presented as medians and ranges for continuous variables and as numbers and percentages for categorical variables.²² Comparisons were made using the Wilcoxon rank sum test and the Fisher exact

test, respectively.²² Serial laboratory tests, oxygen saturation, and temperature were plotted for the 2 groups and compared using repeated-measures analysis of variance.²² Missing data were imputed using the last-value-carried-forward technique.²² Kaplan-Meier methods were used to analyze time to 50% resolution of peak lung involvement and time to cessation of supplemental oxygen; significance was calculated using the log-rank test.²² Patients were censored if at the end of follow-up they had not reached the end point. The data set was created and closed prior to any data analysis. Statistical analyses were completed using SAS statistical software, version 8.2 (SAS Institute Inc, Cary, NC). $P < .05$ was considered significant for all analyses.

RESULTS

Patients

The study population included 16 women and 6 men aged 16 to 86 years. SARS-CoV-associated IgG seroconversion was confirmed in all study patients except 1 who received corticosteroids alone, from whom no convalescent serum sample was obtained. Treatment subgroups did not differ in either demographic or clinical features at post-symptom onset day 7 (TABLE). This comparison was made at day 7 because it is 1 day prior to the median start date of interferon alfacon-1 treatment (day 8; range, days 4-10) and frequently approximates the time of peak disease.²³ The 2 concurrent patients in the comparison group who received high-dose steroids were considered for interferon alfacon-1 therapy but one refused and

Table. Patient Characteristics, Day 7 Clinical Findings, and Additional Treatments*

Characteristics	Interferon Alfacon-1 (n = 9)	Corticosteroids Alone (n = 13)	P Value†
Age	48 (27-56)	42 (16-86)	.79
Female, No. (%)	6 (66.7)	10 (76.9)	.66
Hospital exposure, No. (%)	9 (100)	13 (100)	>.99
Health care workers	9 (100)	7 (53.9)	.46
Comorbid illness, No. (%)‡	1 (11.1)	1 (7.7)	.65
Additional treatment			
Corticosteroids, No. (%)§	9 (100)	13 (100)	>.99
High-dose methylprednisolone, No. (%)	5 (55.6)	2 (15.4)	.08
Maximum steroid dose, mg	500 (50-500)	70 (40-500)	.02
Intravenous immunoglobulin, No. (%)	1 (11.1)	1 (7.7)	.90
Antibiotics, No. (%)	7 (77.8)	3 (33.3)¶	.13
Findings from postonset day 7			
Maximum temperature, °C	38.8 (36.8-39.8)	38.4 (36.5-40)	.43
O ₂ saturation, %	95 (92-99)	93 (92-97)	.17
Abnormal chest radiograph, No. (%)	9 (100)	13 (100)	>.99
Lung involvement, %	20 (5-70)	20 (10-75)	.81
Lymphocytes, cells/μL	800 (400-1290)	840 (440-1680)	.57
Neutrophils, cells/μL	2980 (1260-8160)	5640 (2005-9210)	.18
Platelets, × 10 ³ /μL	183 (125-265)	178 (123-404)	.71
Lactate dehydrogenase, U/L	289 (154-721)	317 (161-883)	.72
Creatine kinase, U/L	102 (32-328)	140 (55-771)	.32
Aspartate aminotransferase, U/L	32 (23-128)	36 (20-121)	.94
Creatinine, mg/dL	0.66 (0.48-0.81)	0.65 (0.52-0.97)	.65

SI conversion factor: To convert creatinine to μmol/L, multiply by 88.4.

*Data are expressed as median (range) unless otherwise indicated.

†P values were estimated by the Wilcoxon rank sum test and, for all categorical data, by the Fisher exact test.

‡Comorbid illnesses included 1 patient with hypertension in each group. There was no incidence of diabetes, cancer, or chronic obstructive pulmonary disease.

§Prednisone and methylprednisolone were tapered.

||High-dose methylprednisolone was started at 500 mg/d for 3 days then tapered; see "Methods" section of text for details.

¶Data available for only 9 patients.

the other was late in the course of disease. The latter patient was transferred from another Toronto hospital and had received intravenous ribavirin, 400 mg every 8 hours, at that hospital for 3 days. Ribavirin was discontinued on admission to NYGH and this patient was intubated and received high-dose methylprednisolone.

Clinical Course and Adverse Events

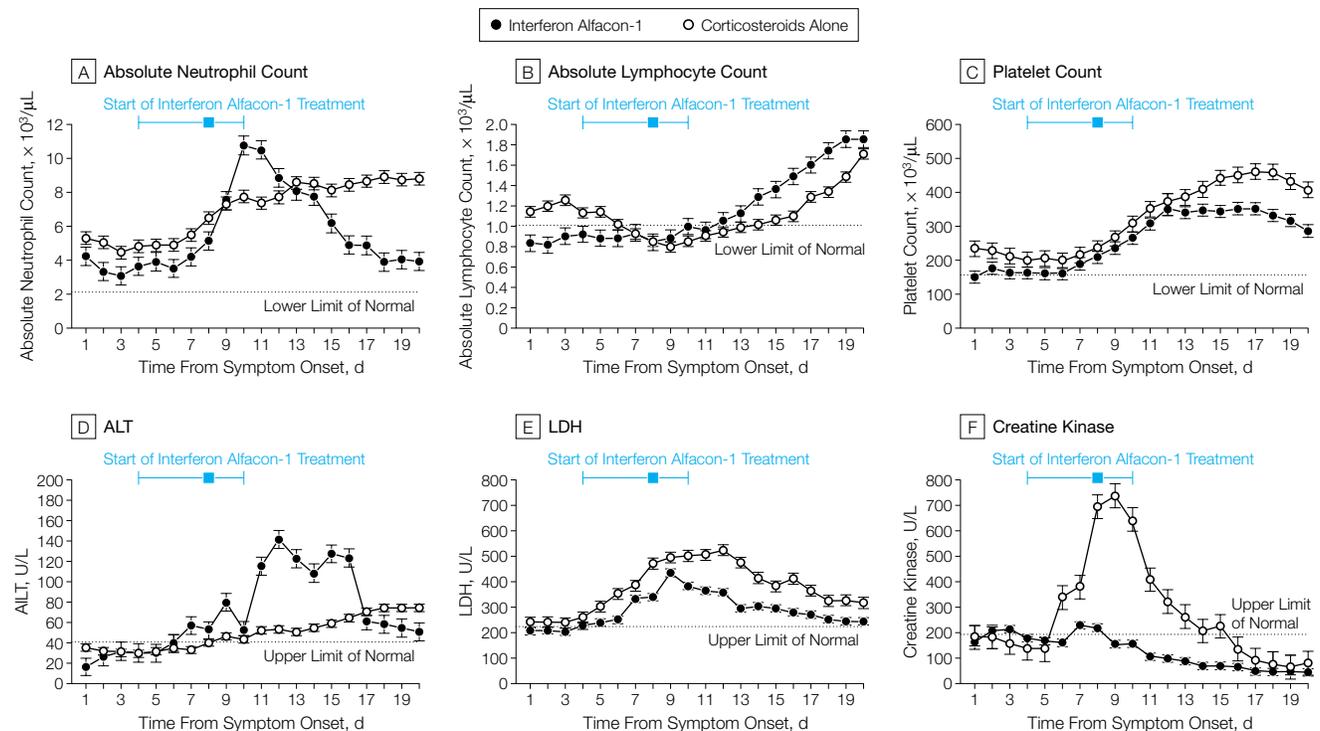
Of the 13 patients treated with corticosteroids alone, 5 (38.5%) were transferred to the ICU, 3 (23.1%) required intubation and mechanical ventilation, and 1 (7.7%) died. Two patients were transferred to the ICU on days 5 and 10 after disease onset and remained in the ICU for 2 and 3 days, respectively. The former patient subsequently died. The other 3 patients were transferred on days 8, 10, and 12 after disease onset and remained there for 10, 14, and 14 days, respectively. These 3 patients were intubated for 9, 5, and 12 days, respectively.

Of the 9 patients treated with interferon alfacon-1, 3 (33.3%) were transferred to the ICU, 1 (11.1%) subsequently required intubation and mechanical ventilation, and none died. Of these patients, 1 who started interferon alfacon-1 on day 8 after disease onset was transferred to the ICU on day 9 and released from the ICU within 24 hours. A second patient received interferon alfacon-1 on day 6 and was transferred to the ICU on day 6, remaining there for 6 days. These 2 patients did not require intubation or ventilation. The third patient started interferon alfacon-1 on day 8 after disease onset, was transferred to the ICU on day 9, was intubated for 14 days, and remained in the ICU for a total of 17 days.

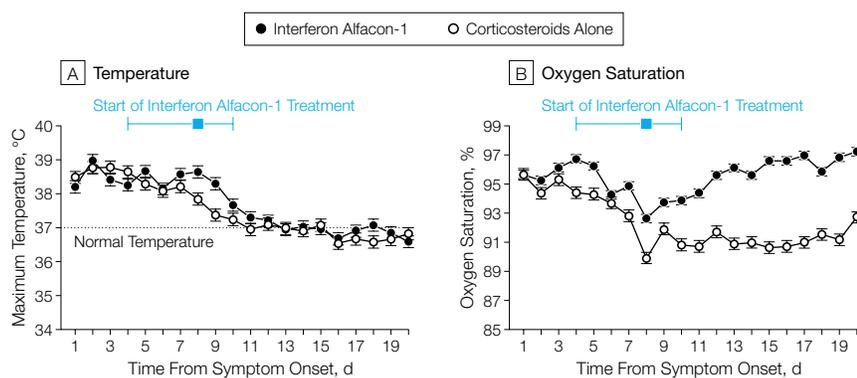
Length of time to discharge was not included as a study outcome because patients receiving interferon alfacon-1 were kept in the hospital for monitoring for the duration of therapy, regardless of clinical status. Patients tolerated inter-

feron alfacon-1 treatment well, with minimal adverse events. The single clinical adverse event reported was fever, which led to discontinuation of the drug in 1 patient. The fever persisted for 1 week after drug discontinuation and was likely due to the underlying disease. None of the patients receiving interferon alfacon-1 developed flulike symptoms, myalgias, or depression. One patient experienced neutropenia with an absolute neutrophil count (ANC) of less than $1000/\mu\text{L}$ on the last day of treatment. Interferon alfacon-1 was generally associated with a minor transient decrease in ANC (FIGURE 1A) and elevation of serum transaminase levels (Figure 1D), both of which resolved within 1 to 2 days of drug discontinuation and appeared to be of no clinical consequence. Decreases in ANC and increases in serum transaminase levels are frequently observed in patients with chronic hepatitis C who are receiving interferon therapy.^{24,25}

Figure 1. Mean Laboratory Test Result Values



ALT indicates alanine aminotransferase; LDH, lactate dehydrogenase. Error bars indicate standard errors. The median interferon alfacon-1 treatment start date was post-symptom onset day 8 (indicated by square; range, days 4-10).

Figure 2. Mean Maximum Temperature and Oxygen Saturation

Error bars indicate standard errors. The median interferon alfacon-1 treatment start date was post-symptom onset day 8 (indicated by square; range, days 4-10).

Follow-up of the 9 interferon alfacon-1 patients to day 60 revealed no evidence of rebound fever or recurrent disease. There was no worsening on chest radiographs, no requirement for supplemental oxygen, and no rehospitalization after cessation of interferon alfacon-1 therapy.

Changes in Clinical Indices

The data in Figure 1 and FIGURE 2 record the changes in mean values of specific clinical measurements and laboratory test results, obtained for both the interferon alfacon-1 and comparison groups over the course of disease. Analysis of these data with the last-value-carried-forward method and with no data imputation yielded identical results. Time-course plots for mean hemoglobin, calcium, total bilirubin, alkaline phosphatase, aspartate aminotransferase, and creatinine values remained within normal range and were similar among all patients (data not shown). The time course for resolution of fever during the course of disease was indistinguishable between the interferon alfacon-1 and comparison groups (Figure 2A).

As in other studies, lymphopenia was observed in all patients.^{23,26,27} However, the absolute lymphocyte counts were indistinguishable between the 2 groups and returned to normal levels during the course of disease (Figure 1B). The ANC increased in the comparison

group (Figure 1A) and initially in the interferon alfacon-1 group. However, continued interferon alfacon-1 treatment was associated with a decrease in ANC that improved after the drug was discontinued. The interferon alfacon-1-treated group also showed less thrombocytosis during recovery than the comparison group (Figure 1C), possibly because of myelosuppression.

Elevated lactate dehydrogenase (LDH) is a consistent laboratory feature of SARS^{6,28} and may represent a marker for lung parenchymal damage. Lactate dehydrogenase increased over time in all patients, but a trend toward faster normalization appeared in the interferon alfacon-1 group (Figure 1E). Creatine kinase (CK) levels, which were highly elevated in the comparison group during the mid course of disease, were minimally altered during the entire course of disease in the interferon alfacon-1-treated patients ($P=.03$ by repeated-measures analysis of variance) (Figure 1F).

Radiographic and Oxygenation Findings

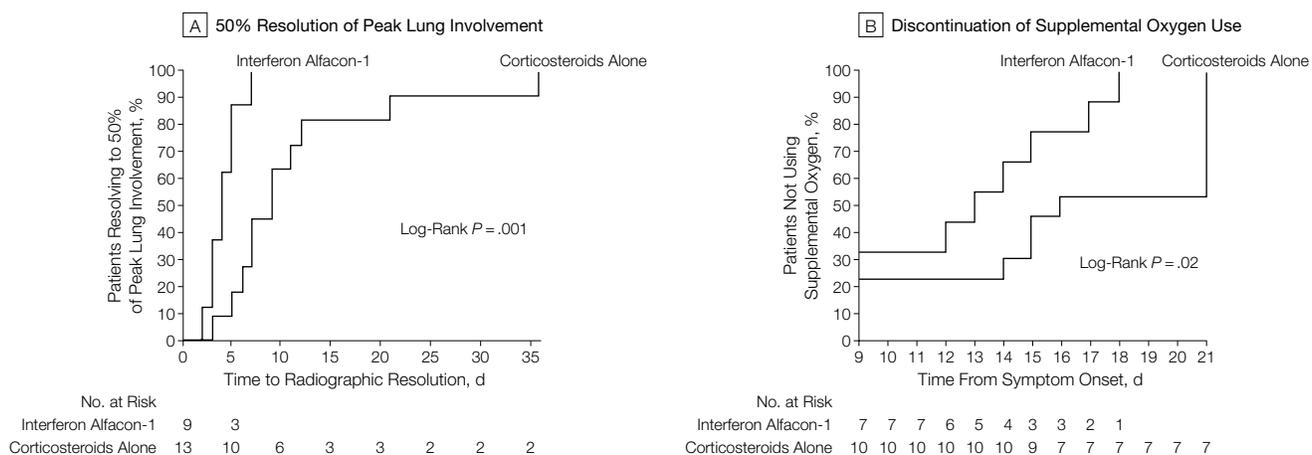
The initial chest radiographs were obtained 3 to 12 days (median, 3 days) and the final radiographs were obtained 7 to 50 days (median, 21 days) after symptom onset. The median number of radiographs obtained per patient was similar in the 2 groups: 11 (range, 7-12) for interferon alfacon-1 patients and 9

(range, 3-12) for the comparison group. The median number of days to peak abnormalities for all patients was 10, with no difference between the interferon alfacon-1 group (median, 11 days; range, 9-12 days) and comparison group (median, 10 days; range, 6-14 days). The median time from peak chest radiographic abnormalities to 50% improvement for interferon alfacon-1 patients was 4 days (range, 2-5 days) and for patients receiving corticosteroids alone was 9 days (range, 4-12 days) ($P=.001$ by log-rank test) (FIGURE 3A).

Consistent with these findings, higher oxygen saturation levels were observed in interferon alfacon-1 patients compared with the comparison group (Figure 2B) ($P=.02$ by repeated-measures analysis of variance). The need for supplemental oxygen resolved significantly faster in interferon alfacon-1 patients than in the comparison group (median, 10 days [range, 0-17 days] vs 16 days [range, 0-21 days]; $P=.02$ by log-rank test). Fifty percent of patients in the comparison group were still receiving supplemental oxygen by day 21, while none of the interferon alfacon-1 patients required oxygen beyond day 17 (Figure 3B).

COMMENT

This article reports the clinical features and outcomes observed in a SARS patient cohort treated with corticosteroids alone or in combination with interferon alfacon-1. These preliminary findings suggest that treatment with interferon alfacon-1 and steroids was associated with more rapid resolution of radiographic lung abnormalities and better oxygen saturation levels than treatment with corticosteroids alone. In addition, in contrast with this comparison group, in whom the disease was associated with considerable increases in CK and LDH levels, interferon alfacon-1 patients showed less increases in CK levels and a more rapid return of LDH to normal levels. As morbidity and mortality in SARS are directly related to pulmonary space infiltration and LDH and CK levels are thought to represent indicators of lung parenchymal

Figure 3. Kaplan-Meier Estimates of Time to 50% Resolution of Peak Lung Involvement and Cessation of Supplemental Oxygen Use

A, Serial chest radiographs were scored for pulmonary abnormalities to quantitate lung involvement, as described in the "Methods" section of the text. B, Two patients in the interferon alfacon-1 group and 3 patients in the corticosteroids alone group never required supplemental oxygen.

damage and poor prognosis, respectively,^{6,23,27} these findings provide preliminary evidence that interferon alfacon-1 therapy may help ameliorate lung parenchymal disease in SARS.

Interferon alfacon-1 therapy was well tolerated by SARS patients and, at least in the group studied herein, did not induce increases in headache, fever, chills, or myalgia—adverse events reported with interferon treatment in other clinical settings.²⁹ The lack of these adverse events is likely due to the concurrent use of steroids in the patient population in this study. Although interferon alfacon-1 therapy was associated with mild neutropenia and some elevation of serum transaminase levels, these changes were clinically insignificant and resolved with drug discontinuation.

The current study was undertaken for the purpose of providing preliminary data on the tolerability, safety, and potential therapeutic benefit of interferon alfacon-1 in SARS patients when administered in combination with corticosteroids. Although steroid use at high or low doses does not appear to induce severe complications in SARS patients, it is currently unclear whether disease course or outcomes are significantly altered by it. However, to conform to the standard of care, corticosteroid treatment was ad-

ministered in all study patients. The findings of improved resolution of radiographic abnormalities, higher oxygen saturation, and reduced CK elevation in interferon alfacon-1 patients cannot, therefore, be attributed solely to interferon alfacon-1, independent of corticosteroids. Emerging data suggest that the clinical progression of SARS involves an initial phase when viral replication contributes to the cytolytic damage and immunopathological response, followed by pathological lung damage caused by an overexuberant host immune response.²³ Interferon alfacon-1 may effectively limit viral load, thereby decreasing the subsequent immunopathological damage. Moreover, interferon alfacon-1 may act synergistically with steroids to immunosuppress the host response.

The dosage of interferon alfacon-1 used in this study was selected in consideration of SARS as an acute viral infection and the consequent aim of achieving high enough interferon alfacon-1 levels to effect viral clearance. Data from studies of patients with hepatitis C treated with interferon alfacon-1 have revealed that daily dosing at 9 μg provides a sustained antiviral response^{21,29} and that effectiveness in terms of viral clearance increases with 15- μg and 30- μg doses.³⁰ It is in this

context that the 9- μg and 15- μg doses were used in the current study. The 15- μg dose appeared to be well tolerated and may prove to be the more appropriate dose to use in SARS treatment. The optimal dose, as well as the effect of monotherapy with interferon alfacon-1 in the absence of steroids for the management of SARS, needs to be further evaluated in clinical studies.

Furthermore, the findings reported herein need to be cautiously interpreted in view of lack of randomization, the retrospective study design, and limited sample size. However, despite the limitations of this open-label, uncontrolled study, these data suggest that interferon alfacon-1 may be of value in the treatment of SARS and indicate that its use for this purpose merits further evaluation. To this end, a protocol for a randomized controlled clinical trial, the primary objective of which is to evaluate the safety and virologic efficacy of interferon alfacon-1 in the treatment of probable and suspected SARS cases compared with observation and supportive therapy, has been submitted to and approved by Health Canada.

Author Contributions: Dr Fish had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Loutfy, Blatt, Fish.

Acquisition of data: Loutfy, Blatt, Siminovitch, Ward,

Wolff, Lho, Deif, LaMere, Chang, Kain, Farcas, Ferguson, Latchford, Lai, Fish.

Analysis and interpretation of data: Loutfy, Blatt, Siminovitch, Ward, Pham, Deif, Lai, Fish.

Drafting of the manuscript: Loutfy, Blatt, Siminovitch, Ward, Wolff, Lho, Pham, Deif, Chang, Kain, Latchford, Dennis, Lai, Fish.

Critical revision of the manuscript for important intellectual content: Loutfy, Blatt, Siminovitch, Fish.

Statistical expertise: Loutfy, Blatt, Fish.

Obtained funding: Siminovitch, Dennis, Fish.

Administrative, technical, or material support: Blatt,

Siminovitch, Ward, Lho, Pham, Deif, LaMere, Chang, Kain, Farcas, Ferguson, Latchford, Fish.

Study supervision: Loutfy, Blatt, Fish.

Funding/Support: This work was funded by a grant from the Canadian Institutes of Health Research (CIHR) and Ontario Research and Development Challenge Fund (ORDCF) to Drs Siminovitch, Dennis, and Fish. Intermune Corp provided the interferon alfacon-1 at no cost. Dr Kain holds a Canada Research Chair, Dr Loutfy is a CIHR postdoctoral fellow (McGill University, Montreal, Quebec), and Dr Siminovitch is a CIHR senior scientist.

Role of the Sponsor: The CIHR and the ORDCF did not contribute in any way to the design and conduct of the study, to the collection, analysis, and interpretation of the data, or to the preparation, review, or approval of the manuscript.

Acknowledgment: We dedicate this article to the memory of Nelia Laroza, a colleague from NYGH who succumbed to SARS. We are grateful to Barbara Mederski, MD, for enabling access to patients at NYGH and to Chris Chalmers, PharmD (Intermune Corp), for expediting the special access program for release of interferon alfacon-1.

REFERENCES

- Centers for Disease Control and Prevention. Updated interim US case definition of severe acute respiratory syndrome (SARS). Available at: <http://www.cdc.gov/ncidod/sars/casedefinition.htm>. Accessed November 18, 2003.
- World Health Organization. Revised case definition of SARS. Available at: <http://www.who.int/csr/sars/casedefinition/en>. Accessed November 18, 2003.
- World Health Organization. Cumulative number of reported probable cases of severe acute respiratory syndrome (SARS). Available at: http://www.who.int/csr/sars/country/table2003_09_23/en. Accessed November 18, 2003.
- Oba Y. The use of corticosteroids in SARS. *N Engl J Med*. 2003;348:2034.
- So LK, Lau AC, Yam LY, et al. Development of a standard treatment protocol for severe acute respiratory syndrome. *Lancet*. 2003;361:1615-1617.
- Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA*. 2003;289:2801-2809.
- Wu W, Wang J, Liu P, et al. A hospital outbreak of severe acute respiratory syndrome in Guangzhou, China. *Chin Med J (Engl)*. 2003;116:811-818.
- Brierley, M, Fish EN. IFN- α / β -receptor interactions to biological outcomes: understanding the circuitry. *J Interferon Cytokine Res*. 2002;22:835-845.
- Samuel CE. Antiviral action of IFNs. *Clin Microbiol Rev*. 2001;14:778-809.
- Levy DE, Garcia-Sastre A. The virus battles: IFN induction of the antiviral state and mechanisms of viral evasion. *Cytokine Growth Factor Rev*. 2001;12:143-156.
- Biron CA. IFNs- α and - β as immune regulators—a new look. *Immunity*. 2001;14:661-664.
- Cornberg M, Wedemeyer H, Manns MP. Hepatitis C: therapeutic perspectives. *Forum (Genova)*. 2001;11:154-162.
- Nguyen MH, Wright TL. Therapeutic advances in the management of hepatitis B and hepatitis C. *Curr Opin Infect Dis*. 2001;14:593-601.
- Higgins PG, Philippotts RJ, Scott GM, Wallace J, Bernhardt LL, Tyrrell DA. Intranasal IFN as protection against experimental respiratory coronavirus infection in volunteers. *Antimicrob Agents Chemother*. 1983;24:713-715.
- Tyrrell DA. The efficacy and tolerance of intranasal IFNs: studies at the Common Cold Unit. *J Antimicrob Chemother*. 1986;18(suppl B):153-156.
- Turner RB, Felton A, Kosak K, Kelsey DK, Meischvitz CK. Prevention of experimental coronavirus colds with intranasal alpha-2b IFN. *J Infect Dis*. 1986;154:443-447.
- Sperber SJ, Hayden FG. Comparative susceptibility of respiratory viruses to recombinant IFNs-alpha 2b and -beta. *J Interferon Res*. 1989;9:285-293.
- Cinatl J, Morgnestern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Treatment of SARS with human IFNs. *Lancet*. 2003;362:293-294.
- Alton K, Stabinsky Y, Richards R, et al. Production, characterization and biological effects of recombinant DNA derived humans IFN- α and IFN- γ analogs. In: De Maeyer E, Schellekens H, eds. *The Biology of the IFN System 1983*. Amsterdam, the Netherlands: Elsevier Science; 1983:119-128.
- Blatt LM, Davis JM, Klein SB, Taylor MW. The biological activity and molecular characterization of a novel synthetic IFN-alpha species, consensus IFN. *J Interferon Cytokine Res*. 1996;16:489-499.
- Melian EB, Plosker GL. IFN alfacon-1: a review of pharmacology and therapeutic efficacy in the treatment of chronic hepatitis C. *Drugs*. 2001;61:1661-1691.
- Friis RH, Stellars TA. *Epidemiology for Public Health Practice*. Gaithersburg, Md: Aspen; 1996.
- Peiris JS, Chu CM, Cheng VC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet*. 2003;361:1767-1772.
- Soza A, Everhart JE, Ghany MG, et al. Neutropenia during combination therapy of IFN alpha and ribavirin for chronic hepatitis C. *Hepatology*. 2002;36:1273-1279.
- Fujimori K, Mochida S, Matsui A, et al. Possible mechanisms of elevation of serum transaminase levels during IFN-beta therapy in chronic hepatitis C patients. *J Gastroenterol*. 2002;37:40-46.
- Lee N, Hui D, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med*. 2003;348:1986-1994.
- Avendano M, Derkach P, Swan S. Clinical course and management of SARS in health care workers in Toronto: a case series. *CMAJ*. 2003;168:1649-1660.
- Poutanen SM, Low DE, Henry B, et al. Identification of severe acute respiratory syndrome in Canada. *N Engl J Med*. 2003;348:1995-2005.
- Pockros PJ, Reindollar R, McHutchinson J, et al. The safety and tolerability of daily IFN alfacon-1 plus ribavirin in the treatment of naive chronic hepatitis C patients. *J Viral Hepat*. 2003;10:55-60.
- Cotler SJ, Layden JE, Neumann AU, Jensen DM. First phase hepatitis C viral kinetics in previous non-responder patients. *J Viral Hepat*. 2003;10:43-49.