A Phase I Study of Recombinant Interferon-β in Patients with Advanced Malignant Disease

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ABSTRACT

To evaluate the safety, toxicity, and maximum tolerated dose (MTD) of IFN β-1a (Rebif, Serono Laboratories, Inc.) in patients with malignant diseases unresponsive to standard therapies and to assess the pharmacodynamics and pharmacokinetics associated with IFN β-1a administration, an open-label, single-center phase I study was designed. Thirty-four patients were enrolled and treated with IFN β-1a. All had measurable solid neoplasms or evaluable hematological malignancies. All patients received a single i.v. bolus dose of IFN-β-1a on day 1, followed 7 days later by daily s.c. injections for 28 consecutive days. Successive groups of three patients received increasingly higher doses (in geometric progression from 1.5 million international units (MIU)/m2 to 24 MIU/m2) until dose-limiting toxicities were noted. Pharmacokinetic and biological studies, including measurement of the activity of 2′,5′-oligoadenylate synthetase (2′,5′-OAS) in peripheral blood mononuclear cells and serum levels of soluble Tac (CD 25) and β-2 microglobulin, were performed on patients who agreed to participate. i.v. and s.c. doses of IFN β-1a up to 24 MIU/m2 were administered. The most frequent adverse events (AEs) were constitutional symptoms. Grade III AEs during i.v. dosing included fever, elevation of bilirubin, and infection unrelated to therapy. No grade IV events were seen. AEs noted during continuous s.c. therapy included fever, liver transaminase increase, albuminuria, fatigue, nausea, myalgia, and rigors. Dose-limiting toxicities were encountered during s.c. dosing at the 24-MIU/m2 and 18-MIU/m2 dose levels and included gastrointestinal toxicity, elevations of aspartate aminotransferase and alanine aminotransferase, and albuminuria. The s.c. MTD was determined to be 12 MIU/m2, although there was great variability in the individual patient’s ability to tolerate IFN β-1a. 2′,5′-OAS activity, thought to be indicative of IFN activity, increased within hours after i.v. and s.c. dosing, with the level remaining persistently elevated during the s.c. daily injections. The highest peak level was attained in the 6-MIU/m2 group. There was no evidence that the increase in 2′,5′-OAS activity decayed with repetitive dosing, nor was there evidence of accumulation in this pharmacodynamic marker. Serum β-2-microglobulin levels showed a modest time- and dose-dependent increase after s.c. administration of IFN β-1a, with the largest increase seen at the 24-MIU/m2 dose level. There were no clear dose-dependent responses noted in soluble Tac serum levels. IFN β-1a was well-tolerated when administered by a single i.v. bolus injection at doses up to and including 24 MIU/m2. Daily s.c. injections for at least 28 days were well-tolerated at doses up to and including 12 MIU/m2, with some patients tolerating doses twice as high as this. The MTD for the i.v. route could not be clearly determined according to the guidelines of the protocol. However, i.v. bolus doses up to 24 MIU/m2 were relatively well-tolerated. For the s.c. route, the MTD was determined to be 12 MIU/m2, but there was great interpatient variability, with some patients able to tolerate higher doses.

INTRODUCTION

Following the initial description of a viral inhibitory factor, termed IFN by Isaacs and Lindenmann in 1957 (1), considerable advances occurred in our understanding of the biology and clinical applications of these proteins. IFNs are a group of naturally occurring proteins with antiviral, antiproliferative, and immunomodulatory properties. Three types of IFNs have been identified in humans, designated as IFN-α, IFN-β, and IFN-γ. IFN-α and IFN-β have been collectively called type I, whereas IFN-γ is also known as type II. The validity of this classification, which was initially based on serological data, was later confirmed by molecular studies that revealed that type I IFNs are closely related (2), sharing ~40% amino acid homology, and acting on cells through a common receptor, with IFN-β binding this receptor with greater affinity (3). Type I IFNs are induced in cells by viral infections and polynucleotides. IFN-α is synthesized mainly in leukocytes, whereas IFN-β is usually produced by fibroblasts. IFN-γ has little homology to the type I IFNs at both the DNA and protein level and is generally produced by T-lymphocytes and natural killer cells. Type I IFNs are encoded on chromosome 9 in close proximity to each other, whereas the gene for IFN-γ is located on chromosome 12 (4).

IFN-β induces antiviral effects in some cells that are resistant or unresponsive to IFN-α, and in vitro studies have shown greater antiproliferative effects for IFN-β than IFN-α as well as qualitative differences in the types of cells affected (5–7). Borden et al. (8) compared the relative antiproliferative activities of type I IFNs in 43 in vitro assays of 25 human cell lines and concluded that in 24 cell lines, the antiproliferative...
The enzyme 2',5'-oligoadenylate synthetase (2',5'-OAS) is induced by IFNs and is a potential marker for predicting clinical response to IFN therapy (9). It causes polymerization of ATP into 2',5'-oligoadenylates, thereby activating an endonuclease capable of cleaving single-stranded RNA. This may be responsible for the inhibition of RNA transcription (9–11). β-2-microglobulin is a cell-surface protein associated with histocompatibility antigens (HLA class I), which transiently rises in serum after the administration of IFNs (12, 13). The Tac protein is one of at least two glycoproteins that form the receptor binding the growth and differentiation factor interleukin 2. In addition to its location on the surface of the cell, Tac is released from activated lymphocytes in a soluble form (14). The level of soluble Tac may be an indicator of the degree of IFN-induced lymphocyte activation. IFNs also induce expression of major histocompatibility class I and II antigens on various cells (15, 16). They also induce protein kinase (17) and protein p78 (18), both of which are important in mediating antiviral and antiproliferative actions. The expression of various tumor-associated antigens such as carcinoembryonic antigen on the surface of human tumor cells is regulated by IFNs (19). IFNs also stimulate a variety of human effector cells (20), augment the expression of glucocorticoid receptors (5), and may have effects in regulation of estrogen and progesterone receptors on tumor cells (21). These properties have led to the investigation of the role of IFNs as novel treatments in neoplastic diseases (22). Clinical trials with IFNs (primarily IFN-α) purified from buffy coat leukocytes began in the 1970s, and in 1980s trials using recombinant IFN-α established its role as a therapeutic agent in chronic myelogenous leukemia, lymphomas, myeloma, melanoma, renal cell carcinoma, and a variety of other tumors.

Various formulations of IFN-β, including natural human IFN-β (Frone, Serono), IFN-β-1a (Rebif, Serono), IFN-β-1a (Avonex, Biogen), and IFN-β-1b (Betaseron, Schering) have been tested and appear less toxic than IFN-α (23). Activity has been demonstrated against herpes infections, human papillomavirus infections, hepatitis B and C, HIV infection, hairy cell leukemia, brain tumors, and multiple sclerosis.

The form of IFN-β-1a used in this study is presently used for treatment of multiple sclerosis in several countries under the name of Rebif (Serono). Dose information is provided in MIU with 12 MIU corresponding to 44 µg.

The pharmacokinetic and pharmacodynamic profiles of IFN-β-1a have been assessed in healthy subjects in both single-dose and multiple-dose studies. After i.v. administration, IFN-β-1a disposition follows a tri-exponential decay model with the following components: t1/2 1 3 min, t1/2 2 40 min, and t1/2 3 21.5 h. Upon repeated s.c. administration, accumulation of ~240% is observed. Total clearance is ~33–55 l/h. Pharmacokinetic profiling included comparing various routes of administration. Bioavailability was variable and averaged around 27–30% after s.c. and i.m. administrations. Serono’s IFN-β-1a (Rebi), when given s.c. or i.m., was found to be bioequivalent to another preparation of glycosylated IFN-β-1a (Avonex, Biogen) given i.m. (24).

IFN-β-1a consists of the native amino acid sequence of natural human IFN-β and is produced in mammalian (Chinese Hamster Ovary) cells. It is glycosylated like the natural protein with physiochemical properties indistinguishable from the fibroblast-derived IFN-β. We undertook this phase I trial to assess the toxicity and possible clinical efficacy of this agent in patients with advanced malignancies and to evaluate biological and pharmacokinetic properties of the drug.

**MATERIALS AND METHODS**

**Eligibility Criteria.** All patients entered in the study had measurable solid neoplasms or evaluable hematological malignancies. They had failed previous standard therapies or had malignancies for which there was no effective therapy. They were between 18 and 70 years of age and were ambulatory with Karnofsky performance scores of ≥60 (equivalent to the Eastern Cooperative Oncology Group performance status of 0–2) within 14 days before the study entry. The pretreatment laboratory results had to be: WBC ≤ 2 × 10⁹/mm³, granulocytes ≥ 1.5 × 10⁹/mm³, platelets ≥ 100 × 10⁹/mm³, total bilirubin ≤ 1.5 mg/dl, prothrombin time ≤ 1.3 × control, and serum creatinine ≤ 2.0 mg/dl. If female, they were neither pregnant nor lactating. Patients had not received cytotoxic chemotherapy, hormonal therapy, immunotherapy, or radiation therapy within 4 weeks before the study entry, except for patients with CML who could not have received any of these therapies within 2 weeks before the study entry. Patients were excluded if they used corticosteroids or nonsteroidal anti-inflammatory agents or had significant nonmalignant systemic disease such as clinically significant cardiac disease (New York Heart Association class III or IV), serious active infection requiring antibiotic therapy, active and inactive autoimmune or immunosuppressive disease, or infection with hepatitis B and HIV.

All patients were informed of the investigational nature of this study and had to provide written informed consent in accordance with institutional and federal guidelines, with the right to withdraw at any time. The study was conducted according to the principles of the declaration of Helsinki and had been approved by the local Institutional Review Board.

**Treatment Protocol.** All patients received a single i.v. bolus injection of IFN-β-1a (IFN-β-1a, Serono Laboratories, Inc.) on study day 1, followed 7 days later by daily s.c. injections of the same dose for 28 consecutive days (days 8–35). The first three patients to enroll received IFN-β-1a at 1.5 MIU/m². Subsequent groups of three patients received increasingly higher doses (in geometric progression) until DLTs were encountered (dose levels: 1.5, 3, 6, 12, 24 MIU/m²). Additional patients were enrolled at a given dose level to replace those who withdrew for reasons other

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2 The abbreviations used are: 2',5'-OAS, 2',5'-oligoadenylate synthetase; CML, chronic myelogenous leukemia; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; AE, adverse event; AST, aspartate aminotransferase; ALT, alanine aminotransferase; SAE, serious AEs; MIU, million international units.
than toxicity. All three patients at a given dose level needed to have received a minimum of 14 days of the 28-day s.c. treatment without the occurrence of DLT before additional patients could be enrolled in the next dose level. MTDs were investigated for the single i.v. administration and the daily s.c. injections. At the end of the 28-day s.c. dosing phase, on day 38, disease evaluation was performed, and patients with stable disease or with objective tumor response were offered the option of maintenance therapy after 1 treatment-free week. During the study, blood samples were taken to determine the pharmacokinetic profiles and biological effects of the i.v. and s.c. doses. Patients were not required to participate in the pharmacokinetic studies. Patient diaries were used to record the date and time of each injection during the s.c. phase, and compliance was checked via the status of returned study drug vials.

**Disease and Toxicity Evaluation.** Patients’ disease status was evaluated before therapy, at day 38, at week 9, and monthly during the maintenance phase using physical examination, tumor markers, and imaging studies as required. For patients with hematological malignancies, peripheral blood smears were taken, and bone marrow examination was performed. For solid tumors, the definitions of tumor response were based upon the standard World Health Organization criteria of complete, partial, and minor response and progressive disease. For CML, standard response criteria was used (25).

**Disease Categories**

- No. of disease sites 2 (1–4)
- Disease duration (yr) 2.2 (0.5–12.5)
- No. of prior therapies 4.5 (2–14)
- No. of disease sites 2 (1–4)
- Disease categories
  - Colorectal 14
  - Breast 3
  - Renal cell 5
  - CML 7
  - Gastrointestinal other 2
  - Chronic lymphocytic leukemia 1
  - Sarcoma 2

**Measurement of Biological Activity.** Activity of 2′,5′-OAS in peripheral blood mononuclear cells and levels of soluble Tac and β2-microglobulin were determined. Intracellular 2′,5′-OAS activity was measured by incorporation of [3H]-ATP into oligoadenylate (26). Samples of peripheral blood mononuclear cells were lyzed with Nonidet buffer and incubated with PolyI:C-agarose beads (Pharmacia) to which the 2′,5′-OAS enzyme binds. The beads were washed and incubated with ATP and [3H]-ATP in buffer, which was converted to the 2′,5′-oligoadenylate product. The product was measured by scintillation counting, and specific activity units were expressed as pico moles of ATP converted per hour per 10⁶ cells. All samples from the same patient were included in the same assay to eliminate interassay variation so that posttreatment levels of intracellular 2′,5′-OAS activity could be compared with pretreatment levels. Assays for the immunological markers, soluble Tac and β2-microglobulin, were performed using the standard methods.

**RESULTS**

**Thirty-Four Patients Enrolled in the Study and Received Treatment with Rebif.** Overall mean age of the patients (± SD) was 52.5 ± 13.6 years (range, 20 to 70 years). There were 14 women and 20 men. At baseline, Karnofsky performance status scores ranged from 70 to 100, with a mean of 94.8 ± 9.1. Patients’ malignancies included breast cancer, chronic lymphocytic leukemia, CML, colorectal and other gastrointestinal cancers, renal cell carcinoma, and sarcoma (Table 1). The average duration of disease was 3 ± 2.6 years, with a range from 0.5 to 12.5 years. All patients had failed at least two prior therapies for their malignancies (ranging from 2 to 14 prior treatments). The most common sites involved with malignancies were bone and bone marrow and liver (each present in 41% of patients), lymph nodes (32%), and lung (29%). All but one patient had received myelosuppressive therapy before study entry. All patients received their intended i.v. dose, and 33 of 34 went on to receive the planned 28 days of s.c. therapy. No patients withdrew from the study due to AEs during the i.v. dosing phase; however, one patient who received the i.v. dose could not enter the s.c. dosing phase due to administrative reasons. Twenty-four of 34 patients (71%) completed the s.c. dosing phase; there were eight withdrawals due to AEs, and one patient decided to discontinue the study. Ten of 34 (29%) went on to a maintenance phase, which lasted from 2 to 188 days.

The most frequent AEs following i.v. administration of Rebif were constitutional symptoms consisting of fever, rigors, headache, myalgia, and fatigue; these were almost always mild to moderate in severity. Fever occurred in 97% of patients, rigors in 68%, headache in 50%, myalgias in 38%, fatigue in 29%, tachycardia in 35%, leukopenia in 32%, and granulocytopenia in 27% of patients following i.v. therapy. DLT, as defined by the study protocol for i.v. dosing, was not reached, although transient grade III fever was observed in one patient in the 12-MIU/m² dose group and in one patient in the 18-MIU/m² dose level at which two or more DLTs occurred. If no more DLTs occurred at this intermediate level, the intermediate level would become the new MTD. Despite using the above guidelines, additional patients could be entered at a particular dose level if more information was needed to establish the DLT clearly.

![Table 1 Patient characteristics and history of malignancies](image-url)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients’ age (yr)</td>
<td>57.5 (20–70)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 20, Female 14</td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>2.2 (0.5–12.5)</td>
</tr>
<tr>
<td>No. of prior therapies</td>
<td>4.5 (2–14)</td>
</tr>
<tr>
<td>No. of disease sites</td>
<td>2 (1–4)</td>
</tr>
<tr>
<td>Disease categories</td>
<td>Colorectal 14, Breast 3, Renal cell 5, CML 7, Gastrointestinal other 2, Chronic lymphocytic leukemia 1, Sarcoma 2</td>
</tr>
</tbody>
</table>

*Values given are number or median (range).*
dose group. This was not defined as MTDs, and i.v. bolus doses up to 24 MU/m² were well-tolerated. Two other grade III AEs noted during the i.v. phase were an elevation of bilirubin (defined as bilirubin increase to 1.5–3.0 normal and considered possibly related to treatment, although the patient’s bilirubin was elevated at baseline) and an infection considered unrelated to treatment.

The most frequent AEs reported during s.c. daily administration were fever, transaminase increase, albuminuria, fatigue, nausea, increased sweating, myalgia, and rigors. Fever occurred in 94%, AST increase in 85%, albuminuria in 67%, fatigue in 79%, nausea in 61%, increased sweating in 49%, myalgia in 67%, rigors in 73%, anorexia in 61%, headache in 52%, injection site reaction in 58%, granulocytopenia in 42%, leukopenia in 39%, and increased ALT in 55% of patients. One patient in the 1.5-MIU/m² group died from cancer progression. There were 14 grade III AEs in the 1.5–12 MIU/m² dose groups during the s.c. phase, of which seven were thought to be related to the therapy. These included several episodes of leukopenia or granulocytopenia. Five patients who received 24 MIU/m² experienced DLTs including grade III vomiting, grade III gastritis, grade III gastrointestinal hemorrhage, grade IV hypertriglyceridemia (defined as triglyceride level > 800 mg/dl), and grade IV increase in AST and ALT (defined as transaminase increase > 10 × normal; Table 2). A total of 10 patients were then enrolled at the 18-MIU/m² dose level. DLTs occurred in four patients at this dose level and included grade IV elevation of AST in three patients and grade III albuminuria (defined as > 10 g/l; Table 2). Elevations of hepatic transaminases to grade IV and recurrent elevations to grade III were not accompanied by clinical problems related to the elevations, and it should be noted that 35% of patients had elevated transaminases at baseline, including three of five patients who had grade III or IV elevations. In addition, 41% of patients had known liver metastases, and 91% took acetaminophen during the study: factors that may have contributed to the elevations. The patient with grade III gastrointestinal hemorrhage had been taking nonsteroidal anti-inflammatory agents, and this was thought to be the etiological factor.

The MTD for s.c. daily injection was determined to be 12 MIU/m². However, there was wide variability in an individual patient’s ability to tolerate IFN-β-1a. The majority of patients in the 18-MIU/m² group (70%) completed the s.c. dosing phase, and 20% continued to the maintenance phase. In the 24-MIU/m²

### Table 2: Dose-limiting toxicities for s.c. administration

<table>
<thead>
<tr>
<th>Rebif dose (MIU/m²)</th>
<th>Duration in study (days)</th>
<th>Dose administered (MIU)</th>
<th>Grade</th>
<th>Adverse event</th>
<th>Action taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>28</td>
<td>29.7</td>
<td>4</td>
<td>AST increase</td>
<td>D/C&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>35</td>
<td>35.1</td>
<td>35.1</td>
<td>3</td>
<td>Albuminuria</td>
<td>None</td>
</tr>
<tr>
<td>48</td>
<td>26.1</td>
<td>26.1</td>
<td>4</td>
<td>AST increase</td>
<td>D/C</td>
</tr>
<tr>
<td>49</td>
<td>29.9</td>
<td>29.9</td>
<td>3</td>
<td>AST increase</td>
<td>Held</td>
</tr>
<tr>
<td>55.0</td>
<td>14</td>
<td>55.0</td>
<td>3</td>
<td>Recurrent vomiting</td>
<td>D/C</td>
</tr>
<tr>
<td>42.0</td>
<td>112</td>
<td>42.0</td>
<td>3</td>
<td>Recurrent gastritis</td>
<td>Held</td>
</tr>
<tr>
<td>48.5</td>
<td>33</td>
<td>48.5</td>
<td>4</td>
<td>Hypertriglyceridemia</td>
<td>D/C</td>
</tr>
<tr>
<td>48.5</td>
<td>21</td>
<td>48.5</td>
<td>4</td>
<td>AST increase</td>
<td>None</td>
</tr>
<tr>
<td>37.7</td>
<td>24</td>
<td>37.7</td>
<td>4</td>
<td>AST increase</td>
<td>None</td>
</tr>
</tbody>
</table>

<sup>a</sup> D/C, discontinued.

### Table 3: Most common severe adverse events (grade III or IV)

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>No. of events</th>
<th>% of severe events</th>
<th>% of all events</th>
<th>No. of patients</th>
<th>% of all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuminuria</td>
<td>15</td>
<td>15</td>
<td>1.0</td>
<td>9</td>
<td>26.5</td>
</tr>
<tr>
<td>AST increase</td>
<td>11</td>
<td>11</td>
<td>0.7</td>
<td>7</td>
<td>20.6</td>
</tr>
<tr>
<td>ALT increase</td>
<td>7</td>
<td>7</td>
<td>0.4</td>
<td>4</td>
<td>11.8</td>
</tr>
<tr>
<td>Anemia</td>
<td>6</td>
<td>6</td>
<td>0.4</td>
<td>4</td>
<td>11.8</td>
</tr>
<tr>
<td>Granulocytopenia</td>
<td>6</td>
<td>6</td>
<td>0.4</td>
<td>5</td>
<td>14.7</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>5</td>
<td>5</td>
<td>0.3</td>
<td>4</td>
<td>11.8</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>5</td>
<td>5</td>
<td>0.3</td>
<td>4</td>
<td>11.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>4</td>
<td>0.3</td>
<td>4</td>
<td>11.8</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>4</td>
<td>4</td>
<td>0.3</td>
<td>2</td>
<td>5.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>3</td>
<td>0.2</td>
<td>2</td>
<td>5.9</td>
</tr>
<tr>
<td>Lactate dehydrogenase increase</td>
<td>3</td>
<td>3</td>
<td>0.2</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2</td>
<td>2</td>
<td>0.1</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2</td>
<td>2</td>
<td>0.1</td>
<td>2</td>
<td>5.9</td>
</tr>
<tr>
<td>Gastritis</td>
<td>2</td>
<td>2</td>
<td>0.1</td>
<td>2</td>
<td>5.9</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2</td>
<td>2</td>
<td>0.1</td>
<td>2</td>
<td>5.9</td>
</tr>
<tr>
<td>Hematuria</td>
<td>2</td>
<td>2</td>
<td>0.1</td>
<td>2</td>
<td>5.9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>2</td>
<td>0.1</td>
<td>2</td>
<td>5.9</td>
</tr>
<tr>
<td>Fever</td>
<td>2</td>
<td>2</td>
<td>0.1</td>
<td>2</td>
<td>5.9</td>
</tr>
</tbody>
</table>
43% of the patients both completed the s.c. dosing phase and entered the maintenance phase.

Quantitatively, a total of 1562 AEs occurred in 34 patients, including 36 SAEs in 7 patients. Most AEs were mild to moderate in severity; 64% were considered grade I, 30% grade II, and 6% grade III. Relatively few grade IV events consisting of nine events (0.6%) were observed. In addition, eight of nine total grade IV events were biochemical abnormalities (elevations of AST, ALT, triglycerides, and lactate dehydrogenase) and were not associated with clinical symptoms. One patient with metastatic colon cancer died 16 days after discontinuing the drug due to disease progression, and this was believed to be unrelated to the therapy. The more common AEs thought to be related to therapy are shown in Table 3.

Disease evaluation was performed before the study and at day 38 and week 9 to identify any responses to treatment and to determine which patients would be eligible for maintenance therapy. During the maintenance phase, disease evaluation was done monthly. Disease evaluation data were collected for 33 of 34 patients, 25 with solid tumors and 8 with hematological malignancies. One patient died from disease progression during the posttreatment follow-up period; with total exposure to IFN-β-1a of 16.8 MIU given over 13 days. A response category was determined for 21 patients with solid tumors, of whom 5 showed stable disease and 16 showed progressive disease. All eight patients with hematological malignancies showed no response.

**Pharmacodynamics and Pharmacokinetics.** 2',5'-OAS activity in the peripheral blood mononuclear cells showed moderate increases within hours after i.v. and s.c. administration in all dose groups, but in particular for the 6 MIU/m² dose levels. Fig. 1 and Fig. 2 present mean intracellular 2',5'-OAS activity as a function of time for each dose group, for the i.v. and s.c. phases, respectively. After i.v. dosing, intracellular 2',5'-OAS activity followed the same pattern for all dose groups. There was an initial increase from baseline levels, with a peak value
occurring between 6 and 24 h after injection. The highest group peak level occurred in the 6-MIU/m² dosing cohort (mean ± SD: baseline, 65.1 ± 7.4 pmol ATP/h/10⁵ cells; peak, 250.5 ± 101.9 pmol ATP/h/10⁵ cells at 12 h). The lowest peak levels occurred in the 18- and 24-MIU/m² cohorts (mean ± SD: peak levels, 85.6 ± 68.6 pmol ATP/h/10⁵ cells at 12 h and 100.7 ± 51.4 pmol ATP/h/10⁵ cells at 6 h, respectively). During s.c. dosing, intracellular 2',5'-OAS activity also followed more or less the same pattern for all dose groups. The most prominent and consistently sustained increases occurred in the 6-MIU/m² dose group; however, firm conclusions about the optimal dose for increasing 2',5'-OAS cannot be drawn due to the small number of patients in each dose group. Importantly, there was no evidence of accumulation or exhaustion of augmented 2',5'-OAS activity with repetitive s.c. administration over 28 days in any dose group. 2',5'-OAS activity is thought to be important in IFN-induced antiviral, antiproliferative, and immunomodulatory actions. The sustained increase after repetitive s.c. dosing supports the rationale for chronic, frequent dosing schedules such as those used in multiple sclerosis and the chronic hepatitides.

Serum levels of β-2-microglobulin and soluble Tac were assessed at baseline and during the i.v. and s.c. dosing phases. Fig. 3 presents mean β-2-microglobulin levels as a function of time. After the i.v. dose, serum β-2-microglobulin appeared to return to baseline levels by day 8 (1 week later). During the s.c. dosing phase, a small progressive increase in serum β-2-microglobulin levels occurred, which appeared to be both time- and dose-dependent and which was most prominent for the 18- and 24-MIU/m² groups. There was a slight decrement in the increased levels for the 24-MIU/m² group near the end of the s.c. dosing phase, but the levels remained above baseline. Changes in soluble Tac were less consistent with dose and time (Fig. 4). There were no clear time- or dose-dependent trends. It should be noted that for both β-2-microglobulin and soluble Tac, there were numerous missing measurements, and substantial inter- and intrapatient variability was observed. It is therefore difficult.
to draw firm conclusions about the effects of IFN-β-1a on these markers.

Pharmacokinetic analysis was carried out in the 29 patients who agreed to participate. However, measurement of IFN-β serum concentrations by bioassay failed to demonstrate an appropriate level of sensitivity to allow pharmacokinetic calculations.

**DISCUSSION**

The study population had advanced malignancies that included a variety of solid tumors and chronic leukemias. Their average age was 52.5 years with a good performance status (mean Karnofsky score of 94.8%). All but one of the patients had had previous myelosuppressive therapy, and all had at least one abnormal laboratory value at baseline. Despite the clinical manifestations of the underlying disease and effects of prior therapies, IFN-β-1a was well-tolerated. All patients completed the i.v. dosing phase, whereas 24 of 34 completed the s.c. dosing phase. During these phases, patients received doses of up to 56 MIU/injection (range, 2.4–56 MIU). Almost 30% of patients entered the maintenance phase, thereby continuing treatment for up to 188 days (range, 2–188 days, mean 42 days) and receiving doses of up to 33 MIU at each injection (range, 2.5–33 MIU).

AEs were primarily mild to moderate in degree, and most were consistent with adverse effects observed with other type I IFNs. Only 9 of a total of 1562 AEs were grade IV, and 89% of these were biochemical abnormalities (increases in AST, ALT, lactate dehydrogenase, and triglycerides) that were not accompanied with clinical manifestations. A dose-dependent increase in SAEs was seen in the two highest dose groups, with 32% of grade III events in the 18-MIU/m² group and 45% in the 24 MIU/m². Thirty three percent of grade IV AEs were in the

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**Fig. 3** Mean β-2-microglobulin (mg/l) ± SD versus time (days).
18-MIU/m² group, and 56% were in the 24-MIU/m² group. The most common SAEs (grade III and IV) were albuminuria, elevated hepatic transaminases, anemia, decrease in WBC, and hypertriglyceridemia. The most common AEs were constitutional symptoms including fever, rigors, fatigue, myalgias, headache, nausea, and anorexia.

DLTs for the s.c. dosing phase were identified only in the 18- and 24-MIU/m² cohorts. After five of seven patients in the 24-MIU/m² cohort experienced DLTs and because no patient in the 12-MIU/m² group had DLTs, patients were enrolled at an intermediate dose level of 18 MIU/m². The DLTs in these dose groups included elevations of ALT and AST, albuminuria, hypertriglyceridemia, and recurrent vomiting (Table 2). The s.c. MTD was, therefore, determined as 12 MIU/m².

IFN β-1a was relatively well-tolerated when administered by i.v. bolus injection at doses up to and including 24 MIU/m² (corresponding to total i.v. bolus doses of up to 56 MIU). Daily s.c. injections for at least 28 days were well-tolerated at doses up to and including 12 MIU/m² (corresponding to daily s.c. doses of up to 27 MIU), the s.c. MTD. Some patients, however, may tolerate doses twice as high as this MTD. Laboratory tests such as clinical chemistry, urinalysis, and complete blood count should be monitored intermittently during treatment. The AEs were transient, were similar to those experienced after treatment with other IFNs, and in general, were easily managed with minimal supportive care. The s.c. dose recommended for phase II studies is 12 MIU/m². i.v. doses up to 24 MIU/m² are well-tolerated.

Moderate increases in the activity of the pharmacodynamic marker, 2',5'-OAS, were noted within hours after i.v. and s.c. dosing, with the level remaining persistently elevated during the s.c. daily injections. These increases appeared to be dose-dependent for dose groups up to and including 6 MIU/m², with the highest peak level attained in the 6-MIU/m² group. However, firm conclusions about the optimal dose for increasing 2',5'-OAS cannot be drawn due to the small number of patients in each dose group. There was no evidence that the increase in 2',5'-OAS activity decayed with repetitive dosing, nor was there evidence of accumulation in this pharmacodynamic marker. Serum β-2-microglobulin levels showed a modest time- and dose-dependent increase after s.c. administration of IFN β-1a, with the largest increase seen at the 24-MIU/m² dose level. There were no clear dose-dependent responses noted in soluble Tac serum levels.

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A Phase I Study of Recombinant Interferon-β in Patients with Advanced Malignant Disease

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