# Phase I Trial of Subcutaneous Recombinant Human Interleukin-12 in Patients with Advanced Renal Cell Carcinoma

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## ABSTRACT

**Patients with advanced renal cell carcinoma were treated in a Phase I trial with escalating doses of recombinant human interleukin-12 (rHuIL-12) given on days 1, 8, and 15 of each 28-day cycle. Treatment in the initial dose scheme consisted of a fixed dose with dose levels of 0.1, 0.5, and 1.0 μg/kg given to cohorts composed of three or six patients. On the basis of the toxicity profile, a second scheme (up-titration) was undertaken wherein rHuIL-12 was escalated for each patient from week 1 to week 2, to a target dose given week 3 and thereafter; cohort target dose levels were 0.5, 0.75, 1.0, 1.25, and 1.5 μg/kg. Fifty-one patients were treated: 32 (63%) had prior cytokine therapy and 19 (37%) had received no prior systemic therapy. The maximum tolerated dose for the fixed dose scheme was 1.0 μg/kg. Dose-limiting toxicities included increase in transaminase concentration, pulmonary toxicity, and leukopenia. The most severe toxicities occurred with the first injection and were milder upon further treatment. With the up-titration dose scheme, the maximum tolerated dose was reached at 1.5 μg/kg, and dose-limiting toxicity consisted of an increase in serum transaminase levels.**

**At the maximum tolerated dose of 1.5 μg/kg, serum IL-12 levels increased to a mean peak level of 706 pg/ml. Serum levels of IFN-γ increased to a mean peak level of about 200 pg/ml at 24 h after the first maintenance dose of 1.5 μg/kg. The best responses were as follows: one patient had complete response, 34 patients were stable, 14 patients showed progression, and 1 patient was inevaluable.**

**In conclusion, rHuIL-12 was relatively well tolerated when administered by s.c. injection. The recommended dose according to the up-titration schedule of rHuIL-12 (μg/kg) for Phase II trials was as follows: cycle 1, 0.1 (day 1), 0.5 (day 8), 1.25 (day 15); cycle 2 onwards, 1.25. Phase II trials of rHuIL-12 were initiated in previously untreated patients with renal cell carcinoma and in patients with melanoma.**

## INTRODUCTION

rHuIL-12[2] is a heterodimeric protein composed of two disulfide-linked subunits having molecular masses of 40 and 35 kDa, respectively (1, 2). IL-12 as a cytokine has been shown to exert a number of regulatory effects on T lymphocytes and NK cells (3, 4). These include (*a*) enhancing the lytic activity of NK/LAK-cells; (*b*) facilitating specific cytolytic T-lymphocyte responses; (*c*) inducing the secretion of IFN-γ by both T and NK cells; and (*d*) promoting the development of $T_H1$-type helper T cells, thereby contributing to the development of cell-mediated immune responses (5–8). Other cell types, including monocytes, macrophages, activated B-cells, dendritic cells, and keratinocytes, also contribute to the biological activity of IL-12 (5–8). One activity of IL-12 that may contribute to an antitumor effect is the ability to inhibit angiogenesis, an effect mediated through the induction of IFN-γ (9).

Interest in biological response modifiers as a treatment for metastatic renal cell carcinoma is fostered by the reproducible, albeit infrequent, responses with IFN-α and IL-2 against this chemotherapy-refractory malignancy (10). The antitumor activities of rHuIL-2 were demonstrated in a large number of murine tumor models, including Renca, a spontaneously arising renal cell carcinoma (8, 11). Treatment of mice bearing murine Renca renal cell carcinoma resulted in tumor growth inhibition, tumor regression, and prolongation of survival; the antitumor effect was superior to IL-2 and IFN-α (8, 11). These data provided the rationale for a Phase I trial of rHuIL-12 in patients with renal cell carcinoma. The schedule of s.c. administration at escalating dose levels of rHuIL-12 given once weekly for 3 weeks was based on single- and multiple-dose toxicology studies performed in cynomolgus monkeys and chimpanzees.[3] Pharmacokinetic and pharmacodynamic parameters were studied, which included assessment of IFN-γ and serum neopterin, an unconjugated pteridine released by macrophages after activation by IFN-γ (12).

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[2] The abbreviations used are: rHuIL-12, recombinant human interleukin-12; IL, interleukin; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase.

[3] Roche, unpublished data.

*Table 1* Dosing schemes of rHuIL-12 (μg/kg)

| Cohort | Cycle 1 | | | Cycle 2 and others, days 1, 8, and 15 | No. of patients | Median no. of cycles (range) |
|---|---|---|---|---|---|---|
| | Day 1 | Day 8 | Day 15 | | | |
| Dose escalation scheme A (fixed dose) | | | | | | |
| I | 0.1 | 0.1 | 0.1 | 0.1 | 3 | 4 (1–9) |
| II | 0.5 | 0.5 | 0.5 | 0.5 | 15 | 4 (1–17) |
| III | 1.0 | 1.0 | 1.0 | 1.0 | 6 | 4 (.3–7) |
| Dose escalation scheme B (2-step up-titration) | | | | | | |
| I | 0.1 | 0.25 | 0.5 | 0.5 | 3 | 6 (2–16) |
| II | 0.1 | 0.5 | 0.75 | 0.75 | 3 | 2 (2–3) |
| III | 0.1 | 0.5 | 1.0 | 1.0 | 3 | 3 (2–4) |
| IV | 0.1 | 0.5 | 1.25 | 1.25 | 6 | 4.5 (2–8) |
| V | 0.1 | 0.5 | 1.5 | 1.5 | 12 | 3 (2–11) |

## PATIENTS AND METHODS

**Patients.** Between April 1995 and November 1996, 51 patients with advanced renal cell carcinoma were entered in this institutional review board-approved Phase I trial. All patients were between 18 and 75 years of age; gave informed consent; had measurable disease; had a Karnofsky performance status ≥80%; had an estimated life expectancy of >4 months; had a WBC count of ≥3000 cells/mm$^3$, a granulocyte count of ≥2000 cells/mm$^3$, a platelet count of ≥75,000 cells/mm$^3$, and a hemoglobin level of ≥10 g/dl; had normal serum bilirubin and transaminase levels and alkaline phosphatase ≤ 2.5 times normal; had a normal serum creatinine concentration in patients without a prior nephrectomy and ≤1.5 times normal in patients with prior nephrectomy; and had a serum calcium level of ≤12.5 mg/dl (≤3.12 mmol/liter). Exclusion criteria included active brain metastases, history of psychiatric disabilities or seizures, clinically significant cardiac abnormalities, chronic obstructive pulmonary disease, prior history of systemic liver disease, active systemic infection, and $T_H1$-mediated autoimmune diseases. Prior systemic therapy was allowed, but patients could not have received more than one previous chemotherapy plus one previous immunotherapy.

**rHuIL-12.** rHuIL-12 was supplied by Hoffmann-La Roche, Inc. (Nutley, NJ) as ready-to-use HSA-free solution in single-dose glass vials containing 10, 100, 500, or 1000 μg of purified rHuIL-12 in 1 ml of sterile solution containing polysorbate 80 (0.2 mg/ml) and 67 mM PBS adjusted to pH 7.0. The vials were stored at 2–8°C and protected from light. rHuIL-12 was administered by s.c. injection using a 25 gauge needle.

**Dose Schedule.** All patients were treated with two cycles of therapy lasting 28 days (Table 1). Each cycle consisted of s.c. injections on days 1, 8, and 15. Treatment was given on an outpatient basis, except that patients were hospitalized for pharmacokinetic studies. On the basis of results of the tumor assessment following cycle 2, patients with a response of stable disease or better received additional cycles of therapy until evidence of progression or unacceptable toxicity.

In the initial dose scheme (scheme A), patients were treated with a fixed dose of rHuIL-12 at planned dose levels of 0.1, 0.5, and 1.0 μg/kg. Cohorts included three patients per dose level until a grade 2 or higher toxicity occurred, with the exception of grade 2 fever or leukopenia and grade 3 or 4 lymphopenia or fever; for these levels and subsequent dose-escalated levels, an additional three patients were entered. The maximum tolerated dose was defined as the level at which two of six patients experienced dose-limiting grade 3 or 4 toxicity.

As a result of observations made during the initial phase of the trial regarding treatment tolerability, a second scheme (scheme B) was initiated in August 1995, after patients were treated on the trial. In this scheme, the dose of rHuIL-12 was escalated for each patient on days 8 and 15 of cycle 1 (Table 1). Subsequent cycles were administered at the day 15 dose level. Target (day 15) dose levels were 0.5, 0.75, 1.0, 1.25, and 1.5 μg/kg. Patients weighing more than 80 kg received a maximum total dose corresponding to a body mass of 80 kg. The number of patients treated per dose level and the maximum tolerated dose was defined as described for dose scheme A.

Patients were monitored by physical examination, complete blood count, and serum chemistry on each day of treatment. Each patient had a reassessment of measurable disease after the second cycle of treatment and then every 4 weeks thereafter. Patients with stable disease had tumor assessments performed every 2 months thereafter. All patients kept a daily log documenting symptoms and medications taken. Response was assessed according to WHO criteria and toxicity according to Common Toxicity criteria.

**Pharmacodynamic and Pharmacokinetic Parameters.** IFN-γ, tumor necrosis factor-α, and neopterin concentrations were measured in the serum of patients at preselected times. Serum samples were obtained at baseline and 10, 24, 48, 72, 96, and 168 h following treatment on day 1 of cycle 1 of treatment scheme A and day 15 of cycle 1 of treatment scheme B.

IFN-γ concentrations in serum were determined by a commercial assay (R&D Systems, Minneapolis, MN). In brief, 50 μl of the assay diluent were added to each well of the microtiter plate. Two hundred μl of standard or sample was added to each well and incubated for 2.5 h at room temperature. Each well was then washed three times with buffer, and any remaining wash removed by blotting it against a clean paper towel or by aspiration. Two hundred μl of IFN-γ conjugate were added and incubated for 2 h at room temperature. Each well was repeatedly washed/aspirated, 200 μl of substrate solution were added, and the samples were incubated for 20 min. Fifty μl of stop solution were added to each well and tapped to ensure thorough mixing. The absorbance of each well was determined within 30 min

using a spectrophotometer set at 450 nm. The interassay variability was <10%, and the limit of detection was 3.0 pg/ml.

Neopterin concentration in serum was measured using a radio-immunoassay that used $^{125}$I-labeled neopterin as a tracer (Incstar, Stillwater, MN). Antineopterin rabbit antibody was incubated with samples, standards, and $^{125}$I-labeled neopterin. After a 1-h incubation at 37°C, antirabbit antiserum from sheep in polyethylene glycol buffer was added and incubated at room temperature for 15 min. Samples were centrifuged, supernatant was decanted, and pellets were counted for radioactivity. The amount of neopterin in sample was inversely proportional to the amount of radioactivity in the pellet. Unknown concentrations were calculated from a standard curve. The assay showed negligible cross-reactivity with other neopterin-like compounds (biopterin, monapterin, and tetrahydroneopterin) and a lower limit of quantitation of 0.2 ng/ml.

Tumor necrosis factor-α concentrations were determined by a quantitative sandwich enzyme-immunoassay technique (R&D Systems). Tumor necrosis factor-α standards and study samples were incubated with antibody bound to a microtiter plate. After washing away unbound substances, an enzyme-linked polyclonal antibody specific for tumor necrosis factor-α was added to the wells. The plates were washed to remove unbound antibody-enzyme reagent, and a substrate solution was added. Color development was proportional to the amount of tumor necrosis factor-α bound in the initial step. Sample concentrations were determined on a standard curve by plotting the absorbance *versus* tumor necrosis factor-α concentration. The lower limit of quantitation of the assay was 15.6 pg/ml.

Serum concentrations of rHuIL-12 were measured at baseline and at 2, 4, 8, 10, 16, 24, 30, 34, 48, and 72 h on days 1–3 of cycle 1 of scheme A (fixed dose) and on day 15 of cycle 1 when first maintenance (target) dose was administered in scheme B (up-titration schedule). rHuIL-12 concentration was measured by a two-step method of antibody capture to ensure specificity followed by a cell proliferation assay. rHuIL-12 was isolated from serum by an affinity technique that involved incubation of samples in sterile tissue culture plates precoated with mouse antihuman IL-12 monoclonal antibody (13).

Samples and rHuIL-12 standards were incubated with the bound monoclonal antibody for 3 h on an orbital shaker at room temperature. After a sterile wash with PBS to remove all nonspecific material, KIT 5/K6 cells were added to each well of the tissue culture plates. After incubation for 66 h, cells were pulsed with [methyl-$^{3}$H]thymidine for six h, and cell proliferation was measured by [methyl-$^{3}$H]thymidine incorporation. Sample values were determined on a standard curve obtained from plotting radioactive counts against IL-12 concentration. The assay had a lower limit of detection of 50 pg/ml of serum using 100-μl aliquots. The interassay precision was 8.0%. rHuIL-12 is stable in serum for 24 h at room temperature. Serum samples were also found to be stable after three freeze/thaw cycles.

Anti-rHuIL-12 antibodies were measured in serum at baseline and periodically thereafter. Anti-rHuIL-12 antibodies were determined by a sandwich enzyme immunological assay. The assay was based on the ability of the multivalent anti-IL-12 antibodies to simultaneously bind rHuIL-12 coated on the wells of microtiter plate and soluble peroxidase-conjugated rHuIL-12. The intra- and interassay variabilities were 11 and 20%, respectively. The level of detection for this assay was 29 ng/ml. The specificity of the assay for anti-IL-12 antibodies was confirmed by the absence of any measured response in serum samples containing antibodies against various irrelevant proteins.

*Table 2* Patient characteristics

| Characteristic | No. (%) |
|---|---|
| Patients | 51 |
| Male/female | 38 (74)/13 (26) |
| Median age (range) | 56 (38–73) |
| Median Karnofsky performance status (range) | 90 (80–90) |
| Prior nephrectomy | |
| Yes | 43 (84) |
| No | 8 (16) |
| Prior therapy | |
| IFN | 14 (27) |
| IL-2 | 6 (12) |
| IFN plus IL-2 with/without 5-fluorouracil or floxuridine | 11 (26) |
| Granulocyte-macrophage colony-stimulating factor plus IL-6 | 1 (2) |
| Chemotherapy (Tallamustine) | 2 (4) |
| Hormonal therapy (Tamoxifen) | 1 (2) |
| Radiotherapy | 6 (12) |
| No systemic therapy | 19 (37)[a] |
| Evaluable sites | |
| Lung | 31 (61) |
| Mediastinum | 9 (18) |
| Retroperitoneal lymph node | 9 (18) |
| Kidney | 5 (10) |
| Adrenal gland | 5 (10) |
| Bone | 5 (10) |
| Liver | 5 (10) |
| Spleen | 2 (4) |
| Peripheral node | 2 (4) |
| Muscle | 1 (2) |
| Skin | 1 (2) |

[a] Includes two patients treated with radiation therapy.

## RESULTS

**Patient Characteristics.** Fifty-one patients were treated with rHuIL-12 (Table 2). The median age was 56 years, and 43 (75%) had a prior nephrectomy. Thirty-two (63%) had prior cytokine therapy (IFN-α, IL-2, or IL-6), and 19 (37%) had received no prior systemic therapy.

**Treatment Administered and Toxicity.** Twenty-four patients were treated with a fixed-dose schedule (scheme A) and 27 were treated with the up-titration schedule (scheme B; Table 1). Fever, fatigue, and a rapid, transient decrease in WBC counts after the first injection were common to all dose levels. The decrease in WBC count included a decrease in lymphocytes and neutrophils; the lymphocyte count decreased to a greater extent. Other frequent adverse events at doses equal to or greater than 0.5 μg/kg were mild to moderate chills, diaphoresis, anorexia, headaches, transient cough, and nausea and vomiting. There were no treatment-related deaths, and none of the patients required intensive care unit support.

With the fixed-dose regimen, the 0.1 μg/kg dose was well tolerated, and there were no grade 3 toxicities (except fever, which was not dose-limiting). One of three patients treated with 0.1 μg/kg rHuIL-12 had a grade 2 increase in serum transami-

*Table 3* Number of patients experiencing selected adverse events in cycle 1, day 1, *versus* cycle 2, day 15 (grades 2, 3, or 4), from fixed dosing scheme A

| | 0.1 μg/kg ($n$ = 3) | | 0.5 μg/kg ($n$ = 15) | | 1.0 μg/kg ($n$ = 6) | |
|---|---|---|---|---|---|---|
| Adverse event | Cycle 1, day 1 | Cycle 2, day 15 | Cycle 1, day 1 | Cycle 2, day 15 | Cycle 1, day 1 | Cycle 2, day 15 |
| Fever | (2, 0) | (0, 0) | (8, 2) | (1, 0) | (4, 0) | (1, 0) |
| WBC | (0, 0) | (0, 0) | (3, 1) | (1, 0) | (2, 1) | (0, 0) |
| ASAT | (1, 0) | (0, 0) | (0, 0) | (0, 0) | (1, 1) | (1, 0) |
| ALAT | (1, 0) | (0, 0) | (1, 0) | (0, 0) | (0, 1) | (0, 0) |

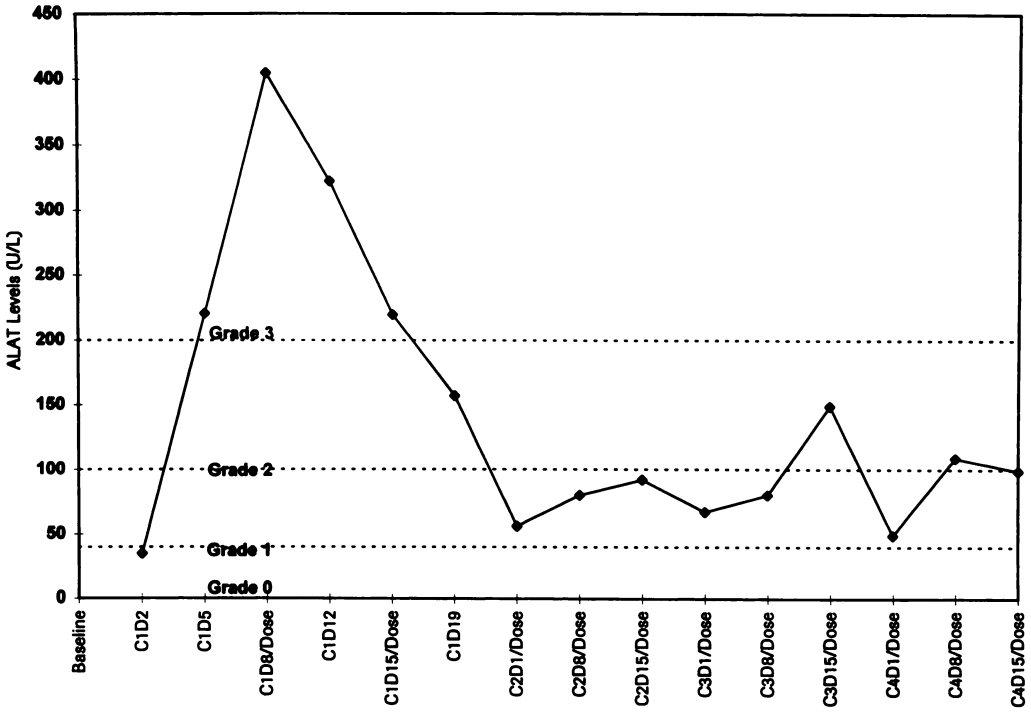


*Fig. 1* Changes in ALAT levels following fixed doses of weekly s.c. administration of rHuIL-12 in a patient (patient 103) at 1.0 μg/kg dose. Increases in transaminase levels were highest after the first dose and decreased on subsequent dosing.

nase concentration in cycle 1, but the patient met grade 1 toxicity pretreatment.

Fifteen patients were treated with a fixed-dose schedule of 0.5 μg/kg. All reported a mild to moderate fever within 36 h of the first injection, and all had mild to moderate increases in serum transaminase concentrations after the first injection. One patient had grade 4 gastrointestinal toxicity. This patient had a distant history of recurrent colitis and a family history of ulcerative colitis undisclosed at study entry. He developed bloody diarrhea during the second cycle, and a colonoscopy showed pancolitis. The patient was taken off the study and improved with medical management that included steroids.

Six patients were treated with a fixed-dose schedule of 1.0 μg/kg; two experienced dose-limiting toxicity composed of a grade 3 increase in transaminase concentration plus grade 4 pulmonary toxicity in one patient and a grade 3 leukopenia in one patient. The pulmonary toxicity was characterized by acute onset of shortness of breath in the setting of fever approximately 40 h following day 1 of cycle 1 treatment during hospital stay. With supplemental oxygen, the patient recovered immediately without sequelae. Evaluation included a chest radiograph, electrocardiogram, and ventilation/perfusion scan, which failed to reveal an etiology. The patient weighed 112 kg, and the relatively high dose of 112 μg of rHuIL-12 may have been a factor; subsequent patients treated on the study were dosed according to a maximum 80 kg weight. At the 1.0 μg/kg dose treatment, fever and leukopenia were more persistent with slower recovery. Nearly all patients treated with 1.0 μg/kg had an increase in transaminase levels 5–10 days after the first injection, but only one patient had grade 3 toxicity.

A comparison of the severity of fever, leukopenia, and elevated serum transaminase concentration according to dose in

*Table 4* Number of patients experiencing selected adverse events in cycle 1 *versus* cycle 2 (grades 2, 3, or 4) from up-titration dosing scheme B

| | 0.5 μg/kg ($n$ = 3) | | 0.75 μg/kg ($n$ = 3) | | 1.0 μg/kg ($n$ = 3) | | 1.25 μg/kg ($n$ = 6) | | 1.5 μg/kg ($n$ = 12) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Adverse event | Cycle 1, day 15 | Cycle 2, day 15 | Cycle 1, day 15 | Cycle 2, day 15 | Cycle 1, day 15 | Cycle 2, day 15 | Cycle 1, day 15 | Cycle 2, day 15 | Cycle 1, day 15 | Cycle 2, day 15 |
| Fever | (0, 0) | (0, 0) | (1, 0) | (0, 0) | (2, 0) | (1, 0) | (2, 0) | (1, 0) | (3, 0) | (0, 0) |
| WBC | (0, 0) | (1, 0) | (1, 0) | (1, 0) | (2, 0) | (1, 0) | (2, 0) | (3, 0) | (4, 0) | (4, 0) |
| ASAT | (0, 0) | (0, 0) | (0, 0) | (0, 0) | (0, 0) | (1, 0) | (0, 0) | (0, 0) | (0, 1) | (0, 1) |
| ALAT | (1, 0) | (0, 0) | (1, 0) | (0, 0) | (0, 0) | (0, 0) | (0, 0) | (0, 0) | (0, 1) | (1, 1) |

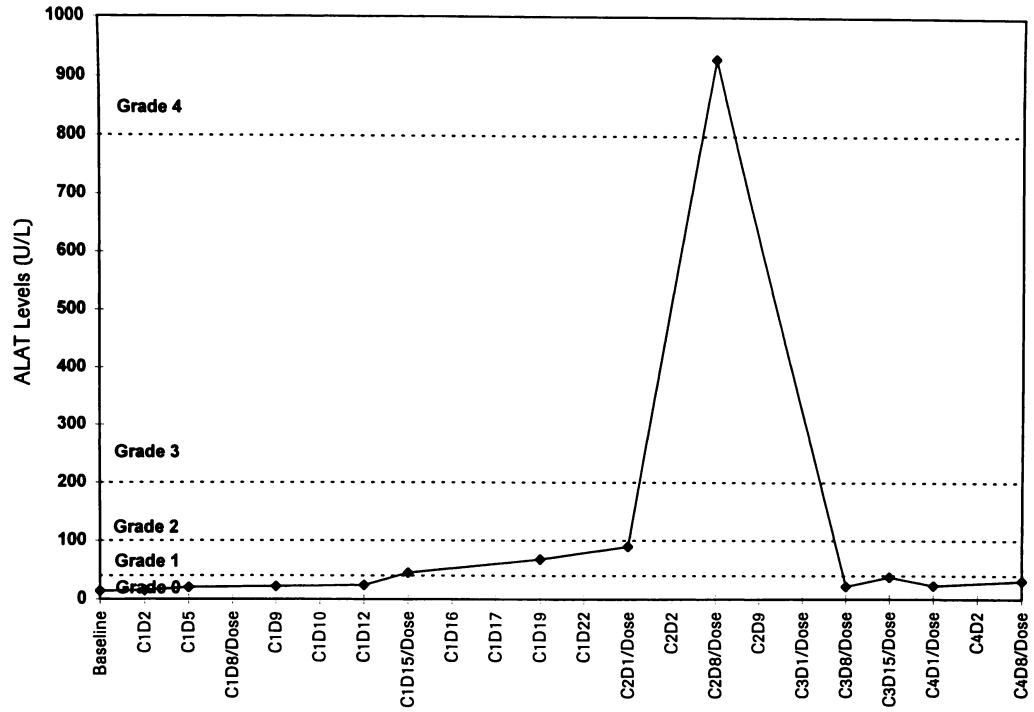


*Fig. 2* Changes in ALAT levels following slow intrapatient dose escalation of rHuIL-12 in a patient (patient 120) at a 1.5 μg/kg maintenance dose. Grade 3 increases occurred after 4 weeks of treatment and decreased on subsequent dosing at 50% level.

cycle 1 *versus* cycle 2 suggested a dose-effect relationship (Table 3). At all dose levels, the most severe toxicities occurred mainly after the first injection and were milder upon further treatment with rHuIL-12 (Fig. 1). Most patients showed only mild (grade 1) fever and other common adverse events (leukopenia and elevated ALAT and/or ASAT) in cycle 2 at all doses. Therefore, the maximum tolerated dose was reached at 1.0 μg/kg with the first dose. Because tolerability improved with subsequent therapy, a slow escalation dosing scheme was followed for a second cohort of patients.

In the second dose scheme, the dose of rHuIL-12 was up-titrated in two steps for each patient following day 1 and day 8 treatments, and patients were treated with the maintenance dose ranging from 0.5 to 1.5 μg/kg from day 15 of cycle 1 until they were taken off study or required a dose reduction. No dose-limiting toxicity was observed in patients treated at target maintenance dose levels of 1.25 μg/kg or less. The maximum tolerated dose was 1.5 μg/kg. At this dose level, two of the first six patients had dose-limiting toxicity. The one patient had grade 4 serum transaminase (ALAT) concentrations during week 2 of cycle 2 at the maintenance dose of 1.5 μg/kg. A second patient had grade 3 serum transaminase elevations following the first injection of the 1.5 μg/kg dose during cycle 1. An additional six patients were treated at this dose level without any dose-limiting toxicity.

The severity of changes in serum transaminase and leukocyte concentrations, as well as fever, was compared between cycle 1 and cycle 2 following escalation doses (Table 4). In contrast to patients treated with the fixed dosing scheme, the slow escalation of rHuIL-12 was better tolerated, although similar adverse events occurred at later times (cycle 2) and at higher doses (Fig. 2).

An additional toxicity observed, albeit not dose-limiting, was stomatitis. Grade 1 mucositis was first noted in two patients

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