The Interleukin-2 Receptor: A Target for Monoclonal Antibody Treatment of Human T-Cell Lymphotrophic Virus I–Induced Adult T-Cell Leukemia


Adult T-cell leukemia (ATL) is a malignancy of mature lymphocytes caused by the retrovirus human T-cell lymphotrophic virus I (HTLV-I). It is an aggressive leukemia with an overall mortality rate of 50% within 5 months; no conventional chemotherapy regimen appears successful in inducing long-term disease-free survival in ATL patients. However, ATL cells constitutively express high-affinity interleukin-2 receptors (IL-2Rs) identified by the anti-Tac monoclonal antibody, whereas normal resting cells do not. To exploit this difference in receptor expression, we administered anti-Tac intravenously (IV) to 19 patients with ATL. In general the patients did not suffer untoward reactions, and in 18 of 19 cases did not have a reduction in normal formed elements of the blood. Seven patients developed remissions that were mixed (1 patient), partial (4 patients), or complete (2 patients), with partial and complete remissions lasting from 9 weeks to more than 3 years as assessed by routine hematologic tests, immunofluorescence analysis, and molecular genetic analysis of T-cell receptor gene rearrangements and of HTLV-I proviral integration. Furthermore, remission was associated with a return to normal serum calcium levels and an improvement of liver function tests. Remission was also associated in some cases with an amelioration of the profound immunodeficiency state that characterizes ATL. Thus the use of a monoclonal antibody that blocks the interaction of IL-2 with its receptor expressed on ATL cells provides a rational approach for treatment of this aggressive malignancy. This is a US government work. There are no restrictions on its use.

THE HYBRIDOMA TECHNIQUE of Kohler and Milstein rekindled interest in the use of antibodies targeted to cell surface antigens to treat cancer patients. Immune-receptor-directed therapy has been applied clinically to an array of human disorders. However, effective therapy using unmodified murine monoclonal antibodies has been elusive because these antibodies are not cytotoxic against human cells and in most cases are not directed against a vital cell surface structure required for tumor cell proliferation and survival. We readdressed this issue using the interleukin-2 receptor (IL-2R) as the target for immune intervention. The scientific basis for this approach using the IL-2R as a target for immunotherapy is that resting normal cells do not express the high-affinity IL-2R, whereas this receptor is expressed by a proportion of the abnormal cells in certain forms of lymphoid neoplasia, select autoimmune disorders, and in individuals rejecting allografts. The IL-2R consists of at least three IL-2-binding peptide chains, as follows: IL-2Rα, a 55-Kd peptide identified by the monoclonal antibody anti-Tac; IL-2Rβ, a 75-Kd subunit; and the recently discovered IL-2Rγ, a 64-Kd protein. Identification and characterization of the IL-2Rα subunit was facilitated by our development of a monoclonal antibody, anti-Tac, that binds to IL-2Rα and prevents the interaction of IL-2 with this subunit. Resting T cells, B cells, and monocytes in the circulation do not display IL-2Rα. In contrast to this lack of IL-2Rα expression in normal resting mononuclear cells, this receptor subunit is expressed by a proportion of the abnormal cells in certain forms of neoplasia including certain T-cell, B-cell, monocytic, and even granulocytic leukemias. Furthermore, the serum concentration of the soluble form of IL-2Rα released by the abnormal cells is increased in patients with these disorders. Specifically, a proportion of the leukemic cells of patients with chronic or acute myelogenous leukemia express IL-2Rα identified by the anti-Tac monoclonal antibody. Furthermore, malignant B cells of virtually all patients with hairy cell leukemia and a proportion of patients with large- and mixed-cell diffuse lymphomas express IL-2Rα. The IL-2Rα is also expressed on Reed-Sternberg cells of patients with Hodgkin's disease and on malignant cells of patients with true histiocytic lymphoma. Similarly, a proportion of patients with cutaneous T-cell lymphomas express the Tac peptide on their malignant cells. Finally, virtually all patients with human T-cell lymphotrophic virus-I (HTLV-I)-associated adult T-cell leukemia (ATL) constitutively express very large numbers of IL-2Rα.

These results suggested that anti-IL-2R antibodies might be effective agents for the treatment of certain neoplastic diseases. We have focused our therapeutic studies of malignancy on the disordered IL-2R expression of a distinct form of T-cell leukemia, ATL. ATL is an aggressive malignancy of lymphocytes displaying a multilobulated nucleus with dense chromatin and expressing a CD3+, CD4+, CD8−, CD7−, and CD25+ (IL-2Rα, Tac+) phenotype. The disease exhibits a striking clustering of cases in certain geographic regions, notably southwestern Japan, the Caribbean basin, northeastern South America, Central America, Sub-Saharan Africa, and to a lesser extent the southeastern United States. The retrovirus HTLV-I is clearly associated with this disease and appears to play a major role in its pathogenesis. Patients with ATL have serum antibodies to HTLV-I and the monoclonal integration of this retrovirus in their circulating malignant cells. Frank ATL generally has its onset in adulthood, 20 to 30 years following initial infection.
infection with HTLV-I. Principal clinical features include moderate lymphadenopathy, hepatosplenomegaly, and skin, central nervous system, and pulmonary involvement; the occurrence of hypercalcemia is characteristic of ATL. Patients with acute ATL manifest a striking degree of immunosuppression and develop opportunistic infections such as Pneumocystis pneumonia and cryptococcal meningitis. The experiences of several clinical oncology groups using combination chemotherapy regimens in patients with this disease have been disappointing. In most chemotherapy series, overall mortality is approximately 50% within 5 months. No conventional treatment program appears successful in inducing long-term disease-free survival in ATL patients.

In our clinical trial, we wished to explore the observation that the normal resting cells of patients with ATL do not display IL-2Rα, whereas the malignant T cells display 10,000 to 35,000 IL-2Rα/cell that are identified by the anti-Tac monoclonal antibody. Thus IL-2Rα-directed immunotherapy using anti-Tac could theoretically eliminate IL-2Rα-expressing leukemic cells while retaining the Tac-nonexpressing normal T cells and their precursors that express the antigen receptors required for normal T-cell-mediated immune responses. In our preliminary studies, we observed that anti-Tac induced a remission in some patients with ATL without associated toxicity. In the present study, the 19 patients with ATL treated with anti-Tac had few untoward reactions related to the immunotherapy and in general did not have a reduction in normal formed elements of the blood. Seven of 19 treated patients had a transient mixed (1), partial (4), or complete (2) remission, with partial and complete remissions lasting from 2 to more than 36 months.

MATERIALS AND METHODS

Patient population. Nineteen patients with histologically confirmed HTLV-I-associated ATL were studied (Table 1). Each of the patients manifested the following features: (1) a histologically confirmed diagnosis of leukemia or lymphoma of mature T cells with polymorphoic indented or lobulated nuclei; (2) intense expression of the Tac antigen (IL-2Rα) on at least 10% of the patient’s peripheral blood, lymph node, or dermal T cells; (3) antibodies to HTLV-I demonstrable in the serum; and (4) omission of cytotoxic chemotherapy and radiation therapy for at least 3 weeks before entry into the trial. Patients with or without previous chemotherapy were eligible for inclusion in this study; 10 patients had failed to respond to prior therapy. Patients with symptomatic central nervous system disease were excluded; however, patients with malignant cells demonstrable in the cerebrospinal fluid were included and received intrathecal methotrexate. The patients ranged in age from 24 to 62 years (mean, 41 years); demographic factors in the patient group are shown in Table 1. Ten patients were male and nine female, 17 were black, one was Hispanic, and one was of Japanese origin, and 10 were from the United States, four were from Jamaica, and one each was from Japan, Cuba, Trinidad, Haiti, and Guyana. Using the criteria of Kawano et al and Yamauchi et al, 11 patients with ATL were in the acute or crisis stage, four manifested ATL lymphoma, and four had chronic ATL.

Therapeutic study plan. Anti-Tac was administered intravenously (IV) over a 2-hour period in 100 mL normal saline containing 5% albumin. In the basic study plan for the initial nine patients, 20 mg anti-Tac was administered IV on two occasions during the first week of therapy, followed by 40 mg on two occasions during the second week. For the subsequent 10 patients, to achieve rapid saturation of the IL-2R, the basic plan involved IV administration of 50 mg anti-Tac on two occasions for each of the first 2 weeks of therapy. Dosing schedules were modified slightly in some patients, and additional 20- or 50-mg doses were administered during subsequent weeks to maintain the saturation of the IL-2R with the anti-Tac monoclonal antibody. Furthermore, in such cases sufficient anti-Tac was administered to yield measurable levels of circulating antibody in the serum of the patient. As noted above, patients with malignant cells in the central nervous system received intrathecal methotrexate.

The criteria for response were as follows: (1) complete response, disappearance of all measurable and assessable disease lasting more than 1 month; (2) partial response, a 50% reduction of leukemic cell count and a 50% reduction in the size of measurable lesions and no increase in the size of any measurable or assessable lesion or appearance of a new lesion for 1 month; (3) mixed response, identical to partial response with the exception that there is the appearance of a new lesion within 1 month in a tissue other than that involved initially; (4) stable disease, less than partial response with no new lesions or less than a 25% increase in any measurable lesion; (5) progressive disease, at least 25% increase in leukemic cell count or an increase of 25% or greater in any measurable lesion. A systems-oriented microcomputer-based patient data management system was devised and implemented in which historical, clinical, and laboratory data were stored and manipulated for analysis (R.P.J. and T.A.W.).

Approval was obtained from the institutional review board for these studies. Informed consent was provided according to the Declaration of Helsinki.

Production of anti-Tac monoclonal antibodies. The anti-Tac monoclonal antibody was produced as described previously by fusion of NS-1 mouse myeloma cells with spleen cells of mice that had been immunized with a cell line derived from an ATL patient. The antibody does not function in complement-dependent cytotoxicity with human plasma nor does it induce antibody-dependent cellular cytotoxicity (ADCC) with human mononuclear cells. However, anti-Tac blocks the interaction of IL-2 with the high-affinity receptors for this lymphokine. Large quantities of the monoclonal antibody were produced by inoculating hybridoma cells into the peritoneal cavity of BALB/c mice and then purifying the mouse IgG2a anti-Tac from the resulting ascites fluid by diethylaminoethyl cellulose chromatography. The purified antibody was dia lyzed against saline, centrifuged, filtered, precipitated with 20% sodium sulfate, and finally diluted in saline at pH 7.4 to a concentration of 2 mg/mL. Each lot of the product was assayed by immunoelectrophoresis in agar plates using antisera to IgG2a, IgG1, and IgM, as well as polyvalent antibodies to most mouse proteins. Lots greater than 98% pure as assessed by these analyses and by high-performance liquid chromatography and sodium decyl sulfate-polyacrylamide gel electrophoresis were used. The monoclonal antibody preparation was sterilized by passage through a 0.22-μm membrane filter (Millipore, Marlborough, MA) by the Pharmaceutical Development Section of the Clinical Center of the National Institutes of Health (NIH) and was shown to be nonpyrogenic and sterile by the Bureau of Biologics.

Immunofluorescence analysis of cell surface phenotype. The phenotype of the leukemic cell population was defined by indirect and direct immunofluorescence performed with mouse monoclonal antibodies using a fluorescence-activated cell-sorter as described previously. Two antibodies (anti-Tac and TgG7/B6) that are directed toward different epitopes of IL-2Rα were used to define the expression of this receptor subunit. Other monoclonal antibodies used include antibodies reacting with HLA-DR (1a-1; Ortho,
Raritan, NJ); human T-cell-associated antigens (CD2, CD3, CD4, CD5, and CD8; Ortho and Becton-Dickinson, Mountain View, CA); CD7 (3A1; a gift from Dr Barton Haynes); and CD45 and CD29 (Coulter Immunology, Hialeah, FL). The fluorescein isothiocyanate (FITC) antiserum IgG reagent was obtained from Coulter Immunology. Histograms for each cell type were integrated to determine the percentage of mononuclear cells that reacted with individual monoclonal antibodies. The absolute number of cells in the circulation per cubic millimeter expressing a particular antigen was determined from the product of (1) circulating white blood cell (WBC) count per cubic millimeter, (2) the proportion of these circulating WBCs that were mononuclear cells as determined by routine hematologic analysis, and (3) the proportion of these mononuclear cells that expressed the antigen under study as assessed by immunocytofluorography.

Molecular genetic analysis of Tcr gene rearrangement and HTLV-I integration. Analysis for clonal Tcr gene rearrangements and for HTLV-I integration were performed as described previously.25,26 High-molecular-weight DNA was extracted from frozen cell suspensions containing approximately 10^6 cells. DNA samples were digested with the restriction enzymes BamHI, EcoRI, HindIII, or PstI (International Biotechnologies, New Haven, CT, and New England Biolabs, Beverly, MA) and were size-fractionated on 0.5% to 0.9% agarose gels. They were transferred by the Southern blot technique to reinforced nitrocellulose paper (Schleicher and Schull, Keene, NH). Hybridization to randomly primed ^32P-labeled DNA probes of the constant regions of the Tcr \( \beta \) gene and the HTLV-I gene were performed, followed by washing at appropriate stringency and radiographs. Nonlymphoid control DNA was analyzed simultaneously to identify germline positions of the Tcr \( \beta \) gene and the HTLV-I gene. The Tcr \( \beta \) gene probe used was a 700-bp EcoRI fragment containing the mouse or human C\( \beta \) region that recognizes both human C\( \beta \) regions. The HTLV-I probe used was the 9-kb Sac1 fragment containing the entire viral genome with the exception of the long terminal repeat (a gift from Dr Flossie Wong-Staal).

**Assay for antibodies to HTLV-I.** The sera of ATL patients were analyzed for antibodies to disrupted and inactivated HTLV-I using an enzyme-linked immunosorbent assay (ELISA) Cellular Products, Buffalo, NY).

**Assay for mouse Ig.** Murine IgG2a anti-Tac levels in the sera of patients were assayed with an ELISA technique using affinity-purified goat antimouse immunoglobulin absorbed onto polystyrene plates at 100 ng/well and washed.39 Bound murine anti-Tac was detected with a goat antimouse immunoglobulin conjugated with alkaline phosphatase (Sigma, St Louis, MO) and compared with a standard curve of anti-Tac antibody.

**Assay for human antimouse anti-Tac antibody.** The serum used in all assays was separated from peripheral blood and stored at \(-20^\circ\)C until used. For detection of human antimouse antibodies (HAMA), the technique described by Schroff et al27 was used, with the exception that anti-Tac was used in lieu of the T101 antibody. Serum antitoglobulin levels for a given patient were considered meaningfully increased when the antitoglobulin level after therapy was greater than twice that in the sample obtained before administration of the mouse monoclonal antibody.

### RESULTS

**Patient characteristics.** Nineteen patients with histologically confirmed HTLV-I-associated ATL were treated with IV administered anti-Tac (Table 1). Four patients had lymphoma-type ATL without circulating malignant cells; the peripheral blood WBC count in the remaining 15 patients before therapy ranged from 3,800 to 230,370 \( \mu \)L (geometric mean, 26,000). Patients with ATL had pretherapy serum soluble IL-2R (sIL-2Ra) levels of 920 to 230,370 \( \mu \)U/mL (mean, 55,744), whereas the upper limit of the normal is 502 \( \mu \)U/mL (mean, 238).28 T-Cell leukemic populations were confirmed to be monoclonal by molecular genetic analysis of the rearrangement of genes encoding the Tcr \( \beta \) chain. Southern blot analysis of the Tcr \( \beta \) receptor gene rearrangement using a radiolabeled probe that hybridizes with the constant region of the Tcr \( \beta \) chain showed a band that was not present in germline tissues, a hallmark of a clonally expanded population of T lymphocytes (Fig 1). Furthermore, Southern blot analysis of HTLV-I proviral integra-

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Type of ATL</th>
<th>Age/Sex/Race</th>
<th>sIL-2R (U/mL)</th>
<th>WBC/µL</th>
<th>Circulating IL-2R/Tac Expressing Lymphocytes/µL</th>
<th>Antibodies to HTLV-I</th>
<th>Serum Ca</th>
<th>Abnormal Liver Function Tests</th>
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<td>1</td>
<td>Acute</td>
<td>35/F/B</td>
<td>147,130</td>
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<td>+</td>
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<td>+</td>
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<td>(&lt;100)</td>
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<td>2.15</td>
<td>+</td>
</tr>
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</tr>
<tr>
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<td>+</td>
<td>8.10</td>
<td>+</td>
</tr>
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<td>6</td>
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<td>44/M/B</td>
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<td>5,500</td>
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<td>+</td>
<td>4.40</td>
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<td>9,910</td>
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<td>21,600</td>
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<td>+</td>
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Abbreviations: B, black; H, Hispanic; A, Asian.
tion in Pst I and EcoRI digests of DNA obtained from the patients defined the clonal integration of HTLV-I proviruses. Clinically, nine patients manifested involvement of the skin. Twelve were hypercalcemic, with a serum calcium level in these cases ranging from 2.65 to 8.1 mmol/L (normal range, 2.05 to 2.5 mmol/L). Mild to moderate liver function abnormalities were demonstrable in 12 of 19 cases.

Using flow cytometric phenotypic analyses of circulating mononuclear cells, we demonstrated that in 13 of 15 cases with leukemia, the predominant mononuclear cell population expressed the CD3⁺, CD4⁺/CD8⁻, CD25⁺ phenotype; phenotypes in the two remaining cases were CD3⁺, CD4⁺/CD8⁺, CD25⁺ and CD3⁻, CD4⁺/CD8⁻, CD25⁺. Circulating mononuclear cells of the patients showed intense expression of the Tac antigen on a relatively homogeneous cell population manifesting high fluorescence intensity (Fig 2). It appears that all of the circulating malignant cells expressed the Tac antigen. Although a small proportion of normal peripheral blood mononuclear cells manifest low-level Tac expression, the pattern observed within the leukemic population is quite distinct from that observed in normal individuals in terms of the homogeneity and intensity of Tac antigen expression (Fig 2). In the 15 leukemic cases, the abnormal cell population did not react with a CD7 (3A1) monoclonal antibody, which reacts with normal T-cell precursors and with at least 70% of normal mature T lymphocytes.

Response of ATL patients to treatment with anti-Tac monoclonal antibodies. The initial basic protocol for anti-Tac therapy involved the administration of 20 mg anti-Tac on two occasions during the first week and 40 mg anti-Tac on two occasions during the second week of therapy for each patient (Table 2). After the second week of therapy, additional doses of 20 or 50 mg anti-Tac were administered to patients who had made an initial clinical response to anti-Tac therapy. It was noted that from 40 to 100 mg anti-Tac had to be administered to the patients to saturate the IL-2Rα expressed by tumor cells. The IL-2Rs on leukemic cells were deemed to be saturated by the infused monoclonal antibody when the cells manifested the following three features: (1) reaction with FITC antimouse IgG; (2) reaction with FITC-labeled 7G7/B6 (an antibody that reacts with IL-2Rα but does not cross-block with anti-Tac); and (3) no binding in direct immunofluorescence analysis with FITC-labeled anti-Tac, since the target antigen was blocked by in

![Image](https://example.com/image1.png)

**Fig 1.** Analysis of Tcr β gene rearrangements to monitor anti-Tac monoclonal antibody treatment in patient no. 5 with ATL using a Tcr β constant region probe (Cβ). The Tcr β constant region genes are on four and 11-Kb EcoRI fragments in placental (germline) DNA as indicated (---). The 11-Kb band contains Cβ1, whereas Cβ2 is present in the 4-Kb band. *An artifactual band at 8.5 Kb that is a result of an incomplete digestion at a site of the Cβ2 locus. Digests of patient peripheral blood DNA during an active phase of the disease 23 days after initiation of therapy yielded a diminished 11-Kb band as well as two nongermline bands (●) that reflect a monoclonal Tcr β pattern of gene rearrangement. This pattern indicates that both alleles for Tcr β in the leukemic clone rearranged into Cβ1. Patient DNA obtained in remission 1,099 days following initiation of therapy did not express the two nongermline bands, thus confirming elimination of the circulating monoclonal population. In the schematic diagram of the germline arrangement of the Tcr β chain gene, we indicate the locations of the BamHI and EcoRI restriction endonuclease sites as well as the Cβ regions recognized by the cDNA probe.
vivo administration of this antibody. In light of these early observations, to achieve a rapid saturation of IL-2R, the basic dosing schedule was altered for the final 10 patients in the group so that 50 mg anti-Tac per patient was administered on two occasions during the first week of therapy and on two occasions during the second week of therapy. Additional doses of 50 mg anti-Tac to maintain receptor saturation were administered to patients who made an initial partial or complete response to therapy. The 19 patients received a total of 23 distinct courses of therapy; there were three to 11 infusions per treatment course (mean, five). Treatment courses ranged from 3 to 57 days (mean, 17), with a total dose of antibody per treatment course ranging from 60 to 500 mg (mean, 225). Maximum levels of mouse antibody achieved in the serum 24 hours after the last therapeutic dose of a treatment course ranged from 595 to 12,230 ng/mL.

**Toxicity.** The 19 patients officially entered into the clinical trial did not have any untoward acute reactions. However, an untoward event that may represent a reaction was observed in one patient with ATL who was treated with anti-Tac off-study under a compassionate protocol exemption. This patient, who was ill on admission with heart failure, hepatosplenomegaly, and multiple effusions, died of respiratory distress following the fifth infusion of anti-Tac; at autopsy, the cause of death was shown to be massive hemorrhagic consolidation of the lungs. One patient developed hives after the second of four anti-Tac infusions. Two patients developed fever to a maximum of 39.1°C following anti-Tac administration. Five patients in six treatment courses manifested an increase in plasma uric acid levels without sequelae; however, the patients were experiencing progressive disease during five of these treatment periods. In general, patients did not manifest hematologic toxicity affecting the normal formed elements of the blood including platelets or polymorphonuclear leukocytes. In the one exception to this generalization, a patient developed a hemolytic anemia and a reduction in the platelet count to 26,000/μL and in the neutrophil count to 380/μL. This patient had leukemic involvement of the bone marrow; he received subsequent doses of anti-Tac without any further untoward reaction noted.

**Tumor response—clinical response.** Twelve of the 19 patients had either a transient response (<2 weeks) or no response to anti-Tac therapy; two of these patients had stable disease, whereas the disease progressed in the remain-

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**Fig 2.** Relative fluorescence intensity of Tac antigen expression was defined by indirect immunofluorescence on the peripheral blood mononuclear cells from (A) patient no. 5 with ATL before therapy; (B) the same patient in remission following completion of anti-Tac therapy; and (C) a normal individual. Circulating mononuclear cells of the patient showed intense expression of the Tac antigen on a relatively homogeneous cell population manifesting high fluorescence intensity before therapy. Following therapy, a small proportion of peripheral blood mononuclear cells of the patient manifested low-level Tac expression. This pattern is quite distinct from that observed during relapse and is comparable to that noted in the normal individual in terms of homogeneity and intensity of Tac antigen expression.
The third patient had a second partial remission lasting 70 days following re-treatment, but then relapsed. Two additional patients, one with chronic ATL and one with acute ATL, developed a complete remission, which lasted for 357 days in the patient with chronic ATL (Fig 3B). The patient with acute ATL is still in a complete remission more than 3 years following entry into remission (Fig 3A).

Initially had hepatosplenomegaly and a peripheral blood WBC count of 41,800/µL that included 23,000 circulating Tac-expressing malignant T cells/µL as assessed by immunofluorescence analysis. The soluble IL-2Rα level was 230,370 U/mL, the highest level observed in this series of ATL patients, and the serum calcium level was 8.10 mmol/L before therapy, more than three times the upper limit of normal. The patient received 400 mg anti-Tac over a 7-week period; by 50 days following initiation of therapy, the patient had undergone a complete remission. Abnormal cells were no longer demonstrable in the circulation. Furthermore, the serum calcium level returned to normal (Fig 4). Before anti-Tac therapy, the patient was anergic; however, when reassessed 2 months and again 1 year posttherapy during a complete remission, the patient manifested positive skin test responses to recall antigens. The patient developed HAMA 4 months following initiation of therapy, but the patient remained in remission. The patient initially had hepatosplenomegaly and a peripheral blood WBC count of 41,800/µL that included 23,000 circulating Tac-expressing malignant T cells/µL as assessed by immunofluorescence analysis. The soluble IL-2Rα level was 230,370 U/mL, the highest level observed in this series of ATL patients, and the serum calcium level was 8.10 mmol/L before therapy, more than three times the upper limit of normal. The patient received 400 mg anti-Tac over a 7-week period; by 50 days following initiation of therapy, the patient had undergone a complete remission. Abnormal cells were no longer demonstrable in the circulation. Furthermore, the serum calcium level returned to normal (Fig 4). Before anti-Tac therapy, the patient was anergic; however, when reassessed 2 months and again 1 year posttherapy during a complete remission, the patient manifested positive skin test responses to recall antigens. The patient developed HAMA 4 months following initiation of therapy, 3 months after entry into the complete remission. Among the six patients with a partial or complete remission following anti-Tac therapy, two had failed to respond to previous chemotherapy, three had hypercalcemia, four had liver function abnormalities, and five were anergic. During the period of partial or complete remission, there was a normalization of the serum calcium level in each case. Furthermore, in the four cases with liver function abnormal-

Table 2. Effect of Anti-Tac Therapy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Previous Therapy</th>
<th>Dose of Anti-Tac Administered (mg)</th>
<th>Toxicity</th>
<th>Development of Anti-Tac Antibodies (HAMA)</th>
<th>Clinical Response/Duration (d)</th>
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<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>150</td>
<td>None</td>
<td>-</td>
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<tr>
<td>2</td>
<td>ProMACE/MOPP</td>
<td>1st course, 160</td>
<td>None</td>
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<tr>
<td>3</td>
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<td>+</td>
<td>PR 70</td>
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<td>CHOP</td>
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<td>None</td>
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<td>None</td>
<td>400</td>
<td>None</td>
<td>+</td>
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<td>9</td>
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<td>220</td>
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<td>PD</td>
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Abbreviations: ProMACE, prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide; COP, cyclophosphamide, vincristine, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; MACOP-B, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone; COP, cyclophosphamide, vincristine, prednisone; CR, complete remission; PR, partial response; SD, stable disease; PD, progressive disease; MR, mixed response.
ANTI-TAC THERAPY OF ATL

Fig 3. (A) Effect of anti-Tac therapy on patient no. 5 with Tac-expressing HTLV-I-associated ATL. (B) Effect of anti-Tac therapy on patient no. 11. Anti-Tac monoclonal antibody was administered IV to the patients at the doses and on the days indicated by solid bars (■). Patient no. 5 (A) initially had a peripheral blood WBC count of 41,800 umL that included 23,000 circulating Tac-expressing malignant cells. The patient received 400 mg anti-Tac over a 7- to 8-week period; by 50 days following initiation of therapy, the patient had undergone a complete remission that has been maintained over the subsequent 3-year period of observation. Patient no. 11 (B) received a total dose of 490 mg anti-Tac. Following anti-Tac therapy, there was a decrease in the number of circulating T cells bearing the Tac antigen from 23,300/umL to normal levels as the patient manifested a complete remission that was maintained for approximately 350 days (■).--- Tac + cells.

Serum calcium levels in patient no. 5. Serum calcium level decreased from the high pretherapy level of 8.1 mmol/L to the normal range following anti-Tac therapy.

Molecular genetic analysis of clinical response. The routine hematologic and immunofluorescence analyses discussed above usually provide valid measures of the efficacy of monoclonal antibody therapy. However, care must be taken when interpreting the immunofluorescence analysis,
because a monoclonal antibody could theoretically cause modulation of its target antigen from the cell surface without leading to death of the cell. Furthermore, one might select for a variant of the leukemic cell that does not express the antigen targeted by the antibody. To address these issues, clinical remissions of T-cell leukemias of the patients were confirmed by molecular genetic analysis of the arrangement of genes encoding the β chain of the Tcr. The rationale for this approach involves the fact that, in contrast to polyclonal T cells, the cells of a monoclonal T-cell tumor share a common Tcr gene rearrangement that can be identified as a novel nongermline band on a radioautograph of a Southern gel analyzed using a Tcr β gene probe. This approach to define clonality is sufficiently sensitive to be used to detect a monoclonal expansion of cells in a mixed-cell population when it represents only 1% of these cells. Complete remissions in two patients with ATL were confirmed by molecular genetic analysis of Tcr β rearrangement (Fig 1). The remission of the T-cell leukemia in these two patients was also confirmed in a parallel molecular genetic analysis of integrated HTLV-I provirions in circulating mononuclear cells (Fig 5). Before therapy, HTLV-I was shown to be clonally integrated into the circulating cells, as assessed on EcoRI and Pst I digests of the peripheral blood T-cell DNA examined with an HTLV-I provirus probe. Using the EcoRI digests, no clonally integrated HTLV-I was demonstrable in peripheral blood cells when the patients were in remission, whereas clonal integration of the virus was again demonstrable in the patient undergoing a relapse. There are no EcoRI restriction sites within the viral genome; hence, the generation of restriction-length fragments containing HTLV-I depends on the recognition of EcoRI sites in host DNA adjacent to viral integration. Therefore only clonally integrated HTLV-I is detectable in EcoRI digests. HTLV-I integration was also assessed on Pst I digests of peripheral blood T-cell DNA. In contrast to EcoRI digests, there are multiple Pst I restriction sites within the complete viral genome generating three identical bands within the viral genome in the presence of both polyclonal and clonally integrated HTLV-I. In patients with monoclonal integration, there were one or two additional bands that depend on the recognition of a Pst I site in host DNA adjacent to viral integration. The patients studied manifested the monoclonal HTLV-I integration pattern before therapy. This band reflecting monoclonal HTLV-I integration was decreased in intensity in three of the four patients undergoing a partial remission and was no longer detectable in the remaining patient in partial remission or in the two patients in complete remission. In patients undergoing a relapse, there was an identity of pretherapy and final relapse HTLV-I integration patterns, confirming the reappearance of the original clone of transformed cells.

Gross abnormalities in the HTLV-I can be detected using the Southern blotting procedure with the HTLV-I probe. In the patient manifesting a sustained complete remission, an abnormal EcoRI and Pst I digestion pattern was observed, thus defining an abnormality in the HTLV-I integrated into the leukemic cell DNA (Fig 5). Such aberrant HTLV-I patterns are common in ATL and represent deletions within the HTLV-I genome.

**Immunologic response** One of the major clinical features associated with ATL is a profound immunodeficiency state affecting both cellular and humoral immunity. Before therapy, only two of the 11 evaluable patients manifested a positive skin test response to one or more of the seven recall skin test antigens assessed with the Merieux Multitest skin test procedure. Furthermore, none of the patients developed HAMA within the 8 weeks following initiation of anti-Tac therapy. None of the patients failing anti-Tac therapy developed positive skin test responses to recall antigens following therapy or made a HAMA response to the infused mouse monoclonal antibody. In contrast, three of the five anergic patients who manifested a partial or complete remission following anti-Tac therapy developed a positive response to one or more recall skin test antigens while in remission. During a subsequent relapse of ATL, there was a loss of this skin test responsiveness to recall antigens. Three of the six patients who underwent a partial or complete clinical remission developed HAMA to the infused anti-Tac at 9, 15, and 23 weeks after starting anti-Tac administration. Although one of these patients produced antibodies to the idotype of anti-Tac, none of the patients produced antibodies that reacted with the isolated Tac peptide or to Tac-expressing cells. Thus, effective IL-2Rα-directed therapy for patients with ATL is associated in some cases with a return of cellular and humoral immune function.

**DISCUSSION** ATL is an aggressive malignancy of mature T cells that accounts for more than half of all lymphomas diagnosed in certain areas of Japan and the Caribbean. In the present study, we treated ATL patients with the anti-Tac monoclonal antibody to exploit the observation that the malignant cells of these patients express the IL-2Rα chain, whereas normal resting mononuclear cells do not express this IL-2R subunit. The 19 patients treated in this study did not have any major untoward reactions related to the immunotherapy. Seven of these patients manifested a transient mixed (one), partial (four), or complete (two) remission, lasting in the patients with partial or complete remissions from 2 to more than 36 months following anti-Tac therapy. This clinical response was defined as the elimination of measurable skin and lymph nodal disease, as well as normalization of routine hematologic and phenotypic tests of circulating cells. There was a normalization of the elevated serum calcium levels and, in some cases, a remission of the immunosuppression that was associated with ATL. These observations support the view that the hypercalcemia and immunosuppression observed in ATL are caused by humoral factors released by the malignant cells. Specifically, the hypercalcemia in ATL appears to be associated with leukemic cell production of parathyroid-related protein. In addition, the abnormal cells produce and secrete large quantities of transforming growth factor-beta 1, a factor that could contribute to the immunosuppression. Finally, the elimination of clonal malignant cells was confirmed by molecular genetic analysis of HTLV-I proviral integration and the Tcr gene rearrangements. Thus, the observed decrease in circulating Tac-antigen-expressing cells does not merely reflect an antibody-mediated modulation
ANTI-TAC THERAPY OF ATL

Fig 5. Southern blot analysis of HTLV-I proviral integration in Pst I and EcoR I digests of DNA obtained from patient no. 5. (A) There are three Pst I restriction sites within the complete HTLV-I genome that on digestion yield three bands of 1.2, 1.8, and 2.5 Kb in the presence of both polyclonally and monoclonally integrated HTLV-I. In patients with monoclonal viral integration, there are one or two additional bands that are encompassed by one Pst I site within HTLV-I and another in host DNA adjacent to the virus. In patient no. 5 before therapy (center lane A) the three Pst I restriction bands present in the complete viral genome were not evident; rather, two other bands of 3.8 and 3.2 Kb were present. This pattern is the hallmark of an aberrant form of HTLV-I that is clonally integrated into the leukemic cell DNA. No HTLV-I was demonstrable in the Pst I digests of the DNA of circulating cells obtained on day 459 following initiation of therapy, supporting the view that this patient was in a complete remission. (B) There are no EcoR I restriction sites within the HTLV-I genome. Therefore the generation of bands representing restriction-length fragments containing HTLV-I depends on the recognition of EcoR I sites in host DNA adjacent to viral integration. Clonal integration of the complete virus is indicated by a band in EcoR I digest that is larger than 9 Kb, the size of a viral genome. In patient no. 5 before therapy, a single band of 8.6 Kb was demonstrable on EcoR I digests of mononuclear cell DNA. The presence of a band is in accord with monoclonal viral integration into the leukemic DNA of the patient. Furthermore, this pattern with a band smaller than 9 Kb confirms that the integrated HTLV-I is abnormal and manifests a deletion within the HTLV-I genome. This band was no longer evident on EcoR I digests obtained during remission (day 459). A schematic diagram of the virus showing Pst I and EcoR I restriction endonuclease sites is shown below.

of this receptor peptide from the cell surface. Furthermore, it does not reflect the selective elimination of IL-2Rα-expressing cells with the retention of a Tac-nonexpressing malignant subpopulation. Anti-Tac used in the treatment of ATL appears more effective than other monoclonal antibodies that were used in early clinical trials for the treatment of cancer. Specifically, in the initial trials reported by 1988, there were only 23 partial and three complete remissions reported in 185 patients entered in 25 clinical trials. Thus, it may be of value to consider the potential mechanisms leading to the antitumor activity observed in seven patients and its failure in the remaining 12 in the present study. Such an analysis may be useful in designing new strategies using anti-IL-2R-directed therapy in clinical circumstances where one might wish to eliminate IL-2R-expressing cells. In the present study, there was no apparent relationship between the clinical response (ie, the difference between seven responding and 12 nonresponding patients) and previous chemotherapy, magnitude of tumor burden, level of circulating mouse immunoglobulin achieved, or initial level of hypercalcemia observed.

The mechanism of action of anti-Tac in eliminating ATL cells has not been fully defined. However, it is clear that the murine anti-Tac monoclonal antibody does not lead to tumor destruction by complement-mediated cytotoxicity, nor does it manifest ADCC with human mononuclear cells, thus seemingly excluding these potential mechanisms of tumor destruction. Another potential general mechanism of antitumor action by a monoclonal antibody is a direct effect on a vital structure present on the surface of the malignant cell, such as a growth factor receptor, which is required for cellular proliferation and survival. This potential mode of antitumor activity provided the scientific rationale for the present study involving patients with ATL; the retrovirus
HTLV-I is the primary pathologic agent in this leukemia. An analysis of HTLV-I and its protein products suggests a potential mechanism for the association between HTLV-I and the constitutive IL-2Rα expression. HTLV-I encodes a 42-Kd protein, now termed tax, that is essential for viral replication. The tax protein also plays a central role in indirectly increasing the transcription of host genes including the IL-2 and especially the IL-2Rα genes involved in T-cell activation and HTLV-I-mediated leukemogenesis. Thus an autocrine model for T-cell growth was considered in which the same leukemic cell produced IL-2 and its receptor. Maeda et al have presented evidence that a subset of patients with ATL have malignant cells in which there is an autocrine growth stimulation by IL-2. In certain IL-2-dependent T-cell lines, the prevention of IL-2 action leads to the death of such cells. Thus in cases where it is effective, anti-Tac might function to inhibit the growth and survival of leukemic cells by preventing IL-2 from interacting with the growth factor receptor (ie, IL-2R) that is required for its action.

Although the use of unmodified anti-Tac for the treatment of ATL was encouraging, 12 of the 19 patients did not manifest even a partial remission; furthermore, six of seven responding patients have relapsed. A number of the explanations suggested for the low therapeutic efficacy of other monoclonal antibodies can be excluded as a major factor limiting anti-Tac activity. One problem observed in other systems is tumor release of sufficient antigen into the circulation to block and prevent the interaction of the antibody with its antigenic target expressed on the tumor cell surface. In fact, a soluble form of IL-2Rα that reacts with anti-Tac is released by Tac-expressing T cells. However, at the doses of this antibody administered the quantity of Tac antigen in the circulation did not prevent anti-Tac from reacting with and saturating its binding sites on circulating leukemic cells. Furthermore, using 111In-radiolabeled anti-Tac in conjunction with unmodified anti-Tac, we have demonstrated that only 2 to 17 mg infused anti-Tac per patient is required to yield circulating bioavailable anti-Tac that can bind to Tac-expressing ATL cells ex vivo (Junghans RP, Carrasquillo J, Waldmann TA, unpublished observations). Thus the 60- to 500-mg total dose of antibody per course used in the present study exceeded the value required to saturate the IL-2R on leukemic cells of the patient.

Another common obstacle to therapeutic activity observed in other systems is the emergence of tumor variants that no longer express the antigen identified by the monoclonal antibody. However, we have never observed the emergence of Tac-nonexpressing ATL variants in patients treated with anti-Tac. Specifically, each of the six patients initially responsive to anti-Tac that subsequently relapsed and became unresponsive to further therapy continued to express the Tac antigen and react with the anti-Tac antibody.

One impediment to therapeutic activity was the development of HAMA by three of the patients. Nevertheless, it should be noted that four of the patients who manifested an initial clinical response but subsequently relapsed and were unresponsive to retreatment never produced HAMA. Furthermore, the patient still in a complete remission is one of the three who produced antibodies to the infused monoclonal antibody. Although the production of HAMA responses by the patients with ATL was not a primary factor preventing antitumor activity, such responses were a major obstacle to long-term effective therapy with murine anti-Tac when it was used in a randomized prospective trial to prevent renal allograft rejection.

Another possible explanation for the failures of anti-Tac therapy in ATL is the observation that in most patients in the aggressive phase of ATL, leukemic cells no longer express meaningful quantities of tax mRNA and do not produce or require IL-2 for their proliferation. That is, only approximately 20% of the patients with ATL have evidence for IL-2-dependent expansion of their leukemic cells. Although in many cases, leukemic cells in the aggressive phase of ATL do not require exogenous IL-2 for their proliferation, they continue to express large numbers of high-affinity receptors that include the IL-2Rα subunit identified by the anti-Tac monoclonal antibody.

We are making a major effort to define the mechanisms underlying the lymphokine-independent growth of ATL cells that continue to constitutively express the IL-2R. Two abnormalities have been defined. In the IL-2–independent ATL cell line examined, we identified a mutation (bp379, leading to a serine-to-phenylalanine change) of the gene encoding the exoplasmic domain of the IL-2Rβ chain. Considerable precedence for constitutive signaling by mutant cell surface receptors, including a mutant erythropoietin receptor, has been reported. The erythropoietin receptor, IL-2Rβ, and IL-2Rγ are members of the same hematopoietin receptor superfamily. To date, no role for the mutation of the IL-2Rβ in the autonomous growth of ATL cells and lines has been defined. A second alteration observed in IL-2–independent ATL cells is a change in the Src-type tyrosine kinase expressed by these cells. IL-2–dependent ATL cell lines, like normal T cells, express the Src-type cytoplasmic tyrosine kinase lck and do not express lyn. In contrast, IL-2–independent ATL cells and lines express lyn and do not express lck. Again, the role of this alteration in the development of IL-2 independence of ATL cells has not been defined.

The therapeutic implications of the aforementioned model of the relationship between abnormalities of IL-2R expression and ATL are that although unmodified murine anti-Tac could be of value in those patients whose malignant T cells still require the autocrine IL-2/IL-2R system for their survival, this agent would no longer be of value in those patients whose leukemic cells had progressed to an autonomous IL-2–independent phase.

Although murine antibodies such as murine anti-Tac are of value in the therapy for some human diseases, their effectiveness is limited because rodent monoclonal antibodies have a short survival time in humans and induce an immune response that neutralizes their therapeutic effect. Furthermore, the responses induced by murine antibodies are limited because the antibodies only weakly recruit human effector elements (ie, they do not function in ADCC with human mononuclear cells) and are relatively ineffective as cytotoxic agents. To circumvent these difficulties, genetically engineered antibody variants of anti-Tac were pro-
duced that combine the rodent hypervariable regions with the human constant and variable framework regions. This humanized anti-Tac is less immunogenic than the murine version, has improved pharmacokinetics, and, in contrast to the parent antibody, manifests ADCC with human mononuclear cells. With the new ADCC activity and the decreased immunogenicity, it is hoped that there will be a substantial improvement in the performance of the antibody in vivo, which should translate into increased efficacy for the treatment of T-cell leukemia/lymphoma.

As noted above, ATL cells and lines derived from them continue to express IL-2R during the late phase of this disease, and different approaches were initiated to arm anti-Tac to augment its cytotoxic activity. Specifically, we have turned to the β- and α-expressing radiouclides as cytotoxic agents that can be conjugated to anti-Tac, thereby generating agents that are effective at eliminating Tac-expressing cells. For example, we bound the β-emitting 86Y to anti-Tac using chelates that did not permit elution of radiolabeled yttrium from the monoclonal antibody. Following efficacy and toxicity studies in subhuman primate cardiac transplantation models, we initiated a dose-escalation trial with 90Y-labeled anti-Tac for the treatment of ATL. At the 5- to 15-mCi doses used, 10 of 15 patients underwent a partial (eight patients) or complete (two patients) remission following 90Y anti-Tac therapy.

In summary, our emerging understanding of the IL-2/IL-2R system opens the possibility for more specific immune intervention. The clinical applications of anti-IL-2R-directed therapy provide a new perspective for the prevention of allograft rejection and for the treatment of autoimmune disorders, and, as discussed in the present study, for the treatment of IL-2R-expressing leukemias and lymphomas.

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The interleukin-2 receptor: a target for monoclonal antibody treatment of human T-cell lymphotrophic virus I-induced adult T-cell leukemia

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