A phase II open-label study of recombinant human interleukin-12 in patients with stage IA, IB, or IIA mycosis fungoides

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Background: Interleukin-12 (IL-12) increases Th_1 cytokines, natural killer (NK) cells, and cytotoxic T-cell activities. Progression of mycosis fungoides is associated with Th_2 cytokines produced by a clonal proliferation of epidermotropic T-helper cells.

Objective: To determine the safety and efficacy of subcutaneous recombinant human IL-12 (rhIL-12) in early mycosis fungoides (MF; stage IA-IIA) in a multi-center, open label clinical trial.

Methods: rhIL-12 was administered biweekly (100 ng/kg for 2 weeks; 300 ng/kg thereafter). A modified severity-weighted assessment tool (SWAT) and the longest diameter of 5 index lesions measured efficacy.

Results: Twenty-three MF patients (stage IA, 12 patients; IB, 9; and IIA, 2) had previously received >3 therapies. Ten of 23 patients (43%) achieved partial responses (PR); 7 (30%) achieved minor responses; and 5 (22%) had stable disease. The duration of PRs ranged from 3 to more than 45 weeks. Twelve (52%) ultimately progressed with mean time to progressive disease of 57 days (range, 28-805). Ten completed 6 months of therapy; 1 completed 24 months. Of patients not completing 6 months of therapy, 6 progressed and 6 others discontinued because of adverse events or withdrew consent. Seventeen patients had treatment-related adverse events that were generally mild or moderate in severity, including asthenia, headache, chills, fever, injection site reaction, pain, myalgia, arthralgia, elevated aspartate and alanine aminotransferase levels, anorexia, and sweating. One patient in PR died of hemolytic anemia, possibly exacerbated by rhIL-12 treatment.

Limitations: The original company was purchased during the conduct of the trial and rhIL-12 is currently unavailable. The quality of life data were not available for inclusion.

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Conflicts of interest: Drs Duvic, Rook, Foss, Wood, Kuzel, and Olsen were principal investigators at their respective centers and therefore received support for the conduct of the clinical trials. Dr Sherman, Mr Laliberté, Dr Ryan, and Ms Zonno were employees of Genetics Institutes or Wyeth.

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Conclusion: Twice-weekly subcutaneously administered rhIL-12 (100 ng/kg escalated to 300 ng/kg) showed antitumor activity with a response rate of 43% in refractory patients. It was relatively well-tolerated in early-stage MF. (J Am Acad Dermatol 2006;55:807-13.)

Interleukin-12 (IL-12) is a heterodimeric cytokine produced by monocytes, dendritic cells, B cells, and other antigen-presenting cells. It is also a potent growth factor for activated T-cells and natural killer (NK) cell proliferation, an enhancer of cytolytic T-cells and NK cell cytotoxicity, and a potent inducer of interferon-gamma (IFNγ) production. IL-12 facilitates the differentiation of T-helper (Th_1) cells and blocks the differentiation of Th_2 cells[1-8]; this selective action has been observed specifically in patients with Sézary syndrome (SS).[9,10]

Mycosis fungoides (MF) is a cutaneous T-cell lymphoma (CTCL) of skin-trafficking malignant $CD4^+$ T-helper lymphocytes.[11-14] Skin lesions are infiltrated with a clonal population of $CD4^+$ T cells with detectable messenger RNA for Th_2-associated cytokines IL-4, IL-5, and IL-10, suggesting that the malignant T cells arise from the Th_2 subpopulation of $CD4^+$ cells.[15-18] The Th_1/Th_2 imbalance that ultimately produces expansion and activation of the Th_2 component appears to predominate in later stages of MF[15,17] and SS.[16,19] In contrast, earlier (patch/plaque as opposed to tumor) stages of MF predominantly possess reactive cytotoxic T-lymphocyte clones expressing primarily the Th_1 (IFN-γ—producing) phenotype, which likely represents the host immune response against the malignant cell population.[20,21]

IL-12 promotes expression of the Th_1 phenotype and its associated immune responsiveness.[4] Conversely, because it inhibits Th_2 lymphocytes, IL-12 may also inhibit MF cells and augment the anti-tumor immune response.[9,16,22-24] Given the observed positive biological and immune actions of IL-12 on Th_1 versus Th_2 T cells, we first examined the safety and efficacy of recombinant human IL-12 (rhIL-12; Wyeth, Cambridge, Mass) in the treatment of MF and SS in an initial phase I study.[23] rhIL-12, administered twice weekly at doses of up to 300 ng/kg, had anti-tumor activity, was relatively well tolerated, and induced complete or partial responses in 5 of 9 evaluable patients (56%).[23,24]

We present results of the first multi-center, phase II study to evaluate the efficacy of rhIL-12 in the treatment of MF.

Abbreviations used:

AE:	adverse event
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
CR:	complete response
CTCL:	cutaneous T-cell lymphoma
IFN-γ:	interferon gamma
MF:	mycosis fungoides
NCI:	National Cancer Institute
NK:	natural killer cell
PD:	progressive disease
PR:	partial response
rhIL-12:	recombinant human interleukin 12
SC:	subcutaneously
SWAT:	skin weighted assessment tool
Th:	T-helper

PATIENTS AND METHODS

Patient selection

Adults with biopsy-proven early MF (stages IA, IB, or IIA), a life expectancy of at least 6 months, adequate hematopoietic, renal, and hepatic function, and Karnofsky performance status index ≥ 70 were enrolled. All patients signed written informed consents approved by the institutional review boards of the different institutions. The study was conducted in accordance with the Declaration of Helsinki and its amendments. Nine centers in the United States participated in the study, which took place between August 1998 and February 2001.

The use of topical agents, phototherapy, or retinoids was not allowed within 1 month of study entry. Patients had to have recovered from the radiation effects of electron beam treatment to be eligible. No more than two systemic chemotherapies within the last year were allowed and patients with a prior history of treatment with purine nucleoside analogs or monoclonal antibodies to T-cells were excluded. The washout time for monochemotherapy was 8 weeks and for multiple chemotherapy agents 12 weeks.

Patients with clinically significant autoimmune disease, gastrointestinal bleeding, uncontrolled peptic ulcer disease, or other significantly compromising illnesses were excluded. Women of childbearing potential and men agreed to use adequate contraception (hormonal or barrier method of birth control) prior to study entry and for the duration of study participation.

Administration of rhIL-12

To minimize toxicity risk, rhIL-12 was administered subcutaneously (SC) at an initial dose of 100 ng/kg twice a week for 2 weeks. Barring any grade 2 or higher toxicity (National Cancer Institute [NCI] Common Toxicity Criteria [CTC] version 1.0), the