MAJOR ARTICLE

Short-Term Safety and Antiretroviral Activity of T-1249, a Second-Generation Fusion Inhibitor of HIV

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T-1249 is a 39-aa synthetic peptide that inhibits fusion of human immunodeficiency virus (HIV) to the host target cell. A 14-day open-label, phase 1/2 dose-escalation monotherapy study of the safety and antiretroviral activity of T-1249 was performed on 115 HIV-1–infected adults. At baseline, the majority of the patients had advanced HIV disease (baseline median $CD4^+$ cell count, 57 cells/μL) and had extensive pretreatment (i.e., pre–T-1249) experience with antiretroviral medications (median, 11 antiretroviral drugs). Patients received T-1249 monotherapy by subcutaneous injection, for 14 days, at doses ranging from 6.25 to 192 mg/day. T-1249 was generally well tolerated, and no dose-limiting toxicity was identified. Injection-site reactions were the most commonly reported adverse event (57%). Dose-dependent decreases in plasma HIV-1 RNA load were observed; the median maximum change from baseline across dose groups ranged from -0.29 $\log_{10}$ copies/mL (95% confidence interval [CI], -0.43 to -0.05 $\log_{10}$ copies/mL) for the lowest dose to -1.96 $\log_{10}$ copies/mL (95% CI, -2.02 to -1.37 copies/mL) for the highest dose. These results indicate that T-1249 is a potent new therapeutic agent for HIV-1 infection.

Conventional antiretroviral medications consist of 3 different classes of drugs: (1) nucleoside and nucleotide reverse-transcriptase inhibitors (NRTIs), (2) protease inhibitors (PIs), and (3) nonnucleoside reverse-transcriptase inhibitors (NNRTIs). Combinations of these agents provide potent suppression of HIV-1 RNA loads and have dramatically improved clinical outcomes for many patients [1]. However, the limitations of current treatment options are increasingly apparent; these include selection for drug-resistant virus [2], significant drug interactions [3], and adverse events associated with treatment [4, 5].

Fusion inhibitors are a new class of compounds with a distinct mechanism of action [6]. These compounds block the conformational change in HIV envelope gp41, which is a step required for fusion of the viral and target cell membranes. Enfuvirtide (formerly "T-20") was the first HIV-1 fusion inhibitor to be tested in patients and is now in clinical use. Analyses at week 24 of phase 3 studies of subcutaneously (sc) administered enfuvirtide (with an optimized background antiretroviral regimen) have demonstrated significant decreases in HIV-1 RNA loads, compared with an optimized regimen alone [7]. Enfuvirtide is administered twice daily, and decreased susceptibility to enfuvirtide has been de-

Received 5 June 2003; accepted 4 September 2003; electronically published 2 March 2004.

Presented in part: 10th Conference on Retroviruses and Opportunistic Infections, Boston, 2003 (abstract 14lb); 11th International HIV Drug Resistance Workshop, Seville, Spain, 2002 (abstract 12); 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, 2002 (abstract H-1075).

Potential conflicts of interest: A.D., C.D., R.D., M.G., T.M., P.R., Y.Z., R.S., and G.D.M. are employees of Trimeris.

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The Journal of Infectious Diseases 2004; 189:1075–83

0022-1899/2004/18905-0015$15.00

scribed to occur after exposure [8–10]. A newer fusion inhibitor with a longer half-life and an improved spectrum of activity, one that includes enfuvirtide-resistant virus isolates, would be a valuable addition to the clinical armamentarium.

T-1249 is a 39-aa peptide that is composed of sequences derived from HIV-1, HIV-2, and simian immunodeficiency virus (SIV) (authors' unpublished data). T-1249 has greater potency in vitro, compared with enfuvirtide, and elicits activity against most enfuvirtide-resistant isolates in vitro [11] and in vivo [12]. The short-term safety and antiretroviral activity of T-1249 were evaluated in a 14-day phase 1/2 dose-escalation study of HIV-1–infected adults (study T1249-101).

SUBJECTS, MATERIALS, AND METHODS

Study population. Eligible patients were HIV-1–seropositive adults who had discontinued antiretroviral therapy at least 14 days before the screening visit. Their plasma HIV-1 RNA loads at screening were required to be ⩾5000 copies/mL, and, for patients in the latter cohorts (cohorts 7–10), the protocol was amended to include an upper limit of 500,000 copies/mL, to avoid values above the dynamic range of the assay and to limit the potential for development of drug resistance. Informed consent was obtained from all patients. Human-experimentation guidelines of the US Department of Health and Human Services and/or those of the authors' institutions were followed in the conduct of clinical research.

Study design. The present study was a multicenter (12 sites) sequential dose-escalation study of T-1249. The study enrollment flow is summarized in figure 1 and is described below. Ten dose cohorts of 12–15 patients each were enrolled. T-1249 was administered sc; an initial formulation of 12.5 mg/mL was used for the first 6 dose cohorts (cohorts 1–6), for whom the daily dose ranged from 6.25 to 50 mg. For total daily doses between 12.5 and 25 mg, patients were randomized to either a 1 dose/day or a 2 doses/day arm. Patients were sequentially assigned to the next highest dose level, in accordance with a predefined dose-escalation schedule that involved a safety review of the first 6 patients at each dose level who had completed the 14-day treatment period.

Upon the availability of a new, more concentrated formulation (48 mg/mL) of T-1249, the study was amended to include 4 additional dose levels (48, 96, 144, and 192 mg/day), each consisting of 1 dose cohort in which T-1249 was administered on a schedule of 1 dose/day (cohorts 7–10). Cohorts 7–10 began enrollment ~1 year after cohorts 1–6 completed treatment.

Study visits occurred at screening and on study days 0, 4, 7, 10, and 14, with a follow-up visit within 14 days of discontinuation of T-1249. Intensive pharmacokinetic analysis was performed on a subset of patients and has been described elsewhere [13]. As part of this analysis, a subset of patients received 1 intravenous (iv) dose of T-1249 7 days before initiation of sc-administered treatment.

Efficacy evaluation. Antiretroviral activity was assessed by measuring plasma HIV-1 RNA load by use of the Roche Amplicor (version 1.0) and/or Roche Amplicor UltraSensitive (version 1.0) HIV-1 monitor assay. The UltraSensitive assay was used for samples with virus loads below the level of quantification of the Amplicor assay (i.e., virus load <400 copies/mL).

Antiretroviral activity was assessed through (1) changes from baseline in $\log_{10}$ plasma HIV-1 RNA load; (2) maximum change from baseline in $\log_{10}$ plasma HIV-1 RNA load; and (3) percentage of patients with a decrease from baseline of at least 1.0 $\log_{10}$ copies/mL HIV-1 RNA, at each study visit and at any time point. The baseline value of HIV-1 RNA for each patient was defined as the mean of the 2 most recent assessments on either the day of or the day before the first sc-administered dose of T-1249. The change from baseline in $CD4^+$ cell counts (absolute and percentage) was analyzed. The baseline value of $CD4^+$ cell count (absolute and percentage) for each patient was determined from the most recent assessment on either the day of or the day before the first sc-administered dose of T-1249.

Genotypic and phenotypic analysis. Genotypic testing of the HIV-1 reverse-transcriptase and protease genes was performed on plasma samples obtained at baseline by use of standard reverse-transcriptase polymerase chain reaction–based methods [14, 15]. Resistance testing of the HIV-1 envelope (Env) is not available for cohorts 1–6. For cohorts 7–10 ($N = 52$), ViroLogic (South San Francisco, CA) performed the genotypic testing of Env and the susceptibility testing of both T-1249 and enfuvirtide, on pretreatment (baseline) and posttreatment (day-14) samples. An entry inhibitor assay was used, by which the gp160 encoding region from a patient's virus isolate was amplified from HIV-1 RNA extracted from plasma samples and was ligated into a recombinant test vector [16]. Viruses that were able to infect both coreceptor (CCR5 or CXCR4) cell lines were classified as dual tropic. To allow comparison with viruses that were able to infect only a single cell line, the IC_{50} or fold change from baseline, from either cell line (CCR5 or CXCR4), was reported; for dual-tropic viruses, the higher of the 2 values was used for analysis.

Evaluation of safety. Safety was monitored through the reporting of adverse events (AEs), routine physical examinations, measurement of vital signs, electrocardiogram measurements, and clinical laboratory testing (including blood chemistry, hematologic tests, coagulation tests, and urinalysis). For cohorts 1–6, all laboratory measurements were performed by Speciality Laboratories (Santa Monica, CA), except for coagulation evaluations, which were performed locally at each site. For cohorts 7–10, all laboratory measurements were performed by Icon Laboratories (Farmingdale, NY). AEs were monitored throughout the study, starting after the first (iv- or sc-administered) dose of T-1249; severity was graded according to the AIDS

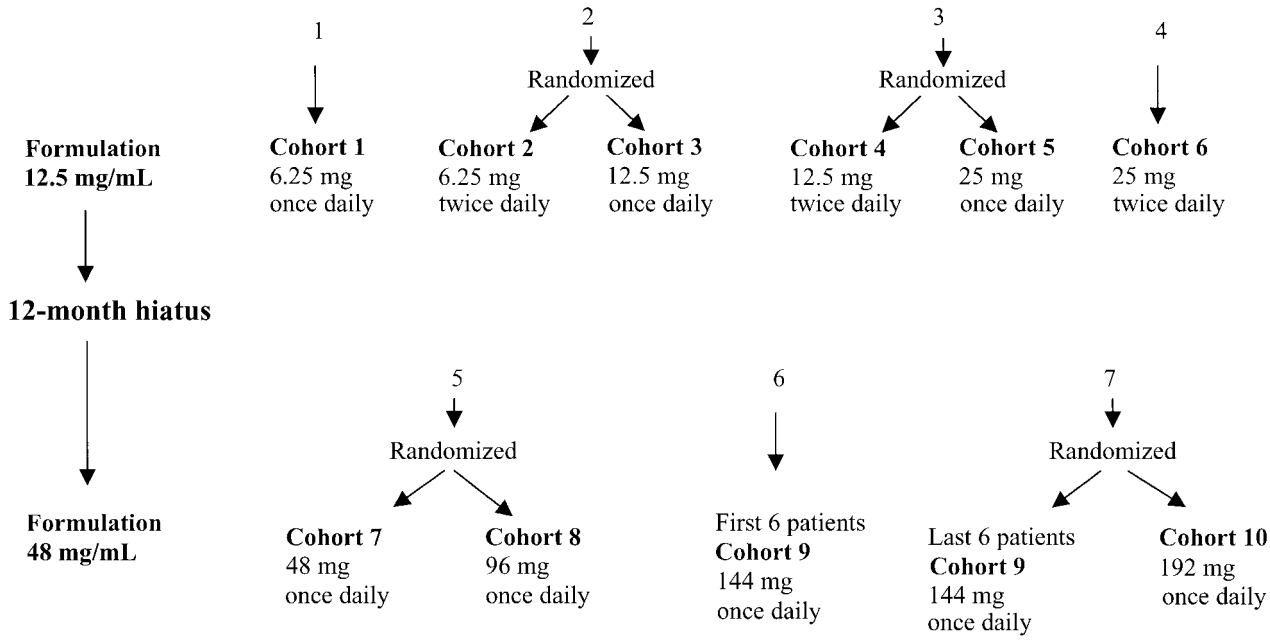

Figure 1. Scheme of enrollment of patients

Clinical Trial Group Toxicity Grading Scale. Local injection-site reactions (ISRs) were recorded separately from AEs, unless they met the definition of a serious AE (SAE). The ISR collection tool for cohorts 1–6 was markedly different from that for cohorts 7–10. For both sets of cohorts, the general pain and discomfort of each reaction was quantitated according to the above-mentioned grading scale. However, for cohorts 1–6, the specific characteristics of the lesions (e.g., induration, erythema, and swelling) were not quantified; the description of the ISR was essentially qualitative. By contrast, in cohorts 7–10, each of the individual characteristics was also quantified, providing more-detailed descriptions of the reactions.

Serum antibody. Serum samples for the detection of specific anti–T-1249 antibodies were obtained on days −7, 0, 14, and at the follow-up visit. Anti–T-1249–specific antibodies were measured by use of a validated, indirect, noncompetitive ELISA. Results were reported as end-point titers, which is a semiquantitative measurement of a patient's antibody response (IgG) to T-1249. A ⩾8-fold change from baseline was considered to be a well-defined change.

Statistical analysis. All data analyses were performed for the intent-to-treat (ITT) population, which was defined as all patients who received at least 1 dose of T-1249. In general, for all patients, data were summarized or tabulated by dose cohort by use of descriptive statistics, for continuous parameters, and number and percentage, for categorical parameters. Ninety-five percent confidence intervals (CIs) for the median change from baseline in $\log_{10}$ HIV-1 RNA load on day 14 and median maximum change from baseline (nadir) in $\log_{10}$ HIV-1 RNA load were constructed [17].

RESULTS

Study Population

A total of 127 patients were enrolled in the present study; of these, 12 (9%) withdrew from the study before administration of T-1249: 7 patients withdrew voluntarily, and the remaining 5 patients developed HIV-related intercurrent illnesses, which required them to withdraw before their first dose of T-1249. Therefore, 115 patients were enrolled in the present study and received at least 1 dose of the study drug (the ITT population). Of these 115 patients, 113 (98%) completed the treatment period, and 2 (2%) discontinued the study prematurely (1 because of an AE [hypersensitivity reaction] and 1 because of failure to comply with the protocol).

Demographic data were similar across all dose cohorts (table 1). The majority of the patients were male (89%), with a median age of 42 years. The median plasma HIV-1 RNA load at baseline was 5.31 $\log_{10}$ copies/mL, and the median $CD4^+$ cell count at baseline was 57 cells/μL.

Nearly all the patients had extensive pretreatment (i.e., pre–T-1249) experience with antiretroviral medications (table 1); in general, the prior use of antiretroviral therapy was similar across dose cohorts. One hundred fourteen (99%) patients had received prior antiretroviral treatment, with a median exposure to 11 antiretroviral agents. Nearly all (99% and 97%, respec-

Table 1. Demographic and baseline characteristics (intent-to-treat [ITT] population).

Characteristic	Dose level, dose frequency (no. of persons in ITT population)										
	6.25 mg/day, 6.25 mg once daily (*N* = 11)	12.5 mg/day		25 mg/day		50 mg/day, 25 mg twice daily (*N* = 11)	48 mg/day 48 mg once daily (*N* = 14)	96 mg/day, 96 mg once daily (*N* = 13)	144 mg/day, 144 mg once daily (*N* = 12)	192 mg/day, 192 mg once daily (*N* = 13)	All cohorts, all patients (*N* = 115)
		6.25 mg twice daily (*N* = 9)	12.5 mg once daily (*N* = 12)	12.5 mg twice daily (*N* = 9)	25 mg once daily (*N* = 11)						
No. of injections per day	1	2	1	2	2	4	1	2	3	4	
Sex, no. (%)											
Male	10 (91)	7 (78)	12 (100)	9 (100)	9 (82)	11 (100)	11 (79)	10 (77)	12 (100)	11 (85)	102 (89)
Female	1 (9)	2 (22)	0 (0)	0 (0)	2 (18)	0 (0)	3 (21)	3 (23)	0 (0)	2 (15)	13 (11)
Age, median (range), years	44.0 (28–50)	40.0 (25–64)	41.0 (30–57)	39.0 (33–59)	40.0 (34–57)	37.0 (32–46)	38.0 (34–55)	42.0 (34–56)	44.5 (34–55)	41.0 (27–52)	41.0 (25–64)
Baseline HIV-1 RNA load, median (range), $\log_{10}$ copies/mL	4.92 (4.28–5.65)	5.57 (4.89–6.00)	5.40 (3.78–6.00)	5.54 (4.34–6.00)	5.54 (4.94–6.00)	5.47 (4.59–5.91)	5.32 (4.02–5.90)	5.30 (3.69–6.00)	5.32 (4.52–5.64)	5.05 (4.35–5.51)	5.31 (3.69–6.00)
Baseline absolute $CD4^+$ cell count, median (range), cells/μL	142 (5–320)	31 (5–659)	24 (6–918)	64 (5–475)	70 (8–313)	57 (6–379)	27 (3–880)	79 (5–809)	38 (5–402)	129 (8–375)	57 (3–918)
Prior no. of antiretrovirals											
No.[a]	11	8	12	9	11	11	14	13	12	13	114
Median (range)	9.0 (4–15)	11.5 (7–13)	10.5 (5–15)	11.0 (2–15)	11.0 (5–16)	11.0 (9–14)	12.5 (5–15)	12.0 (3–15)	11.0 (5–15)	12.0 (5–15)	11.0 (0–16)

[a] No. of patients who had pretreatment (i.e., pre–T-1249) experience with antiretroviral medications.

tively) patients had received NRTIs and PIs, and most (90%) had received NNRTIs.

Measurements of Efficacy

Antiretroviral activity. The median virus load changes from baseline for each cohort are presented in figure 2. There was minimal change in plasma HIV-1 RNA loads in cohorts 1–3 at day 14, whereas, in the other cohorts, there was a median decrease from baseline of at least 0.4 $\log_{10}$ copies/mL. In cohorts 4, 5, and 7, the decrease in median HIV-1 RNA load leveled off at day 7 and did not decrease further after this visit. In contrast, in cohorts 6, 8, 9, and 10, median virus load continued to decrease from baseline through day 10. In general, there was a distinct dose-response relationship, in which administration of higher daily doses resulted in greater antiretroviral responses.

The median maximum change from baseline (nadir) demonstrated a clear dose-response relationship; the 2 highest-dose cohorts (144 and 192 mg/day) experienced the greatest antiretroviral response, with median nadir values of −1.87 (95% CI, −2.23 to −1.45 $\log_{10}$ copies/mL) and −1.96 $\log_{10}$ copies/mL (95% CI, −2.02 to −1.37 $\log_{10}$ copies/mL), respectively. Furthermore, the percentage of patients who experienced a maximum decrease of ⩾1.0 $\log_{10}$ copies/mL in HIV-1 RNA load increased from 0% (cohorts 1–3; 6.25–12.5 mg/day) to as high as 92% (cohorts 8 and 9) and 100% (cohort 10), suggesting that doses of ⩾96 mg/day elicit substantial antiretroviral activity. In an analysis presented elsewhere [18], results of multiple linear-regression analyses demonstrated that maximum antiretroviral responses were directly correlated with daily dose of T-1249 but not with other factors, such as baseline $CD4^+$ cell count, reverse-transcriptase and protease resistance mutations, and prior exposure to antiretroviral therapy.

Analysis of $CD4^+$ cell count. Figure 3 depicts the absolute median change in $CD4^+$ cell count from baseline to day 14, for each treatment cohort. The first 4 treatment cohorts showed no statistically significant increase in $CD4^+$ cell count over the treatment period. In contrast, cohorts 5–10 experienced increases in $CD4^+$ cell count over the 14-day treatment period, with medians ranging from 23 (cohort 8) to 69 (cohort 9) cells/μL.

Genotype and phenotype of HIV-1 envelope gp41. Preliminary in vitro selections for HIV-1 variants resistant to T-1249 have yielded several virus isolates with reduced in vitro sensitivity to T-1249, compared with that of their parental isolates (authors' unpublished data). In those isolates, several genotypic changes have been identified within the gp41 heptad repeat (HR) 1 region, including V38E, Q40K, Q41H, Q41R, and N43K. A total of 52 patients in cohorts 7–10 received at least 1 dose of T-1249; baseline and day-14 gp41 genotypic results were obtained for paired samples from 39 (75%) of those patients; and baseline and day-14 T-1249 (and enfuvirtide) phenotypic results were obtained for paired samples from 38 (73%) of those patients.

At baseline, viral Envs from 48 patients in cohorts 7–10 exhibited an in vitro geometric mean IC_{50} for T-1249 of 0.088 μg/mL (range, 0.015–0.409 μg/mL). In contrast, day-14 viral Envs from the 40 patients with available results had a geometric mean IC_{50} for T-1249 of 0.125 μg/mL (range, 0.013–10.52 μg/mL). Five (13%) of 38 patients with paired genotypic and phenotypic results receiving T-1249 experienced genotypic changes at day 14 that have been shown to be associated with reduced susceptibility to T-1249 (V38E and Q40K; table 2). Four of these 5 patients also experienced a decrease of >4-fold in susceptibility to T-1249 and enfuvirtide while receiving treatment. Additionally, all 5 patients had baseline HIV-1 RNA loads >5.0 $\log_{10}$ copies/mL (100,000 copies/mL), and, although all 5 patients experienced an initial decrease in virus load, by day 14, 3 patients (patients A, C, and E) experienced a rebound in plasma HIV RNA load of ⩾0.5 $\log_{10}$ copies/mL from their nadir

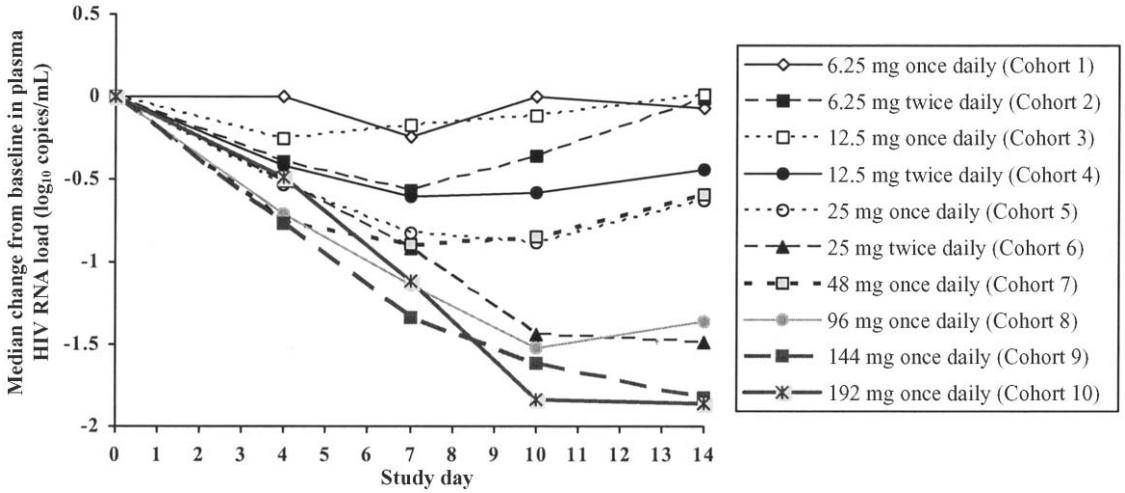

Figure 2. Median change in plasma HIV-1 RNA ($\log_{10}$ copies/mL) from baseline (intent-to-treat population)

value. In patient B, the virus load did not change from day 10 to day 14; the viral response was <1.0 $\log_{10}$ copies/mL and remained >100,000 copies/mL throughout the study.

Safety and tolerability. In general, T-1249 was well tolerated at all dose levels, throughout the 14-day treatment period. A maximum tolerated dose was not achieved. Most patients (77%) experienced at least 1 AE, excluding nonserious ISRs. The incidences of AEs, by body class system, across the T-1249 treatment groups did not suggest a dose-related effect (table 3). Overall, for the 115 patients, the most frequently reported AEs were headache (14%), pyrexia (14%), rash (13%), lymphadenopathy (10%), and oral candidiasis (10%). Selected hematologic (including coagulation) and blood-chemistry parameters were monitored, with no apparent trends or dose-dependent laboratory toxicities observed (data not shown).

Overall, a total of 66 patients (57%) experienced at least 1 ISR. For cohorts 1–6, 25 (40%) of 63 patients experienced at least 1 ISR, and the overall frequency of ISRs decreased with increased time receiving treatment (data not shown). All except 1 ISR was assessed to be grade 1 (mild) in intensity. The major symptoms reported were pain (21%) and discomfort (14%), and associated signs included erythema (11%), induration (3%), and swelling (1%). For cohorts 7–10, in which the higher concentration of T-1249 (48 mg/mL) was used, there was an increase in the number of reported ISRs with the increased daily dose of T-1249 (table 4). Most ISRs were of mild to moderate severity, on the basis of pain and discomfort, and the most common signs/symptoms were erythema (50%) and sc induration (42%).

Two patients experienced an SAE suggestive of an allergic reaction. On day 4 of treatment with 25 mg of T-1249 twice a day, 1 patient (in cohort 6) experienced a hypersensitivity drug reaction, with signs and symptoms including fever, mouth ulcers, diffuse maculopapular rash, and mildly increased levels of transaminases. T-1249 was permanently discontinued, and, within 6 days, symptoms improved. The second patient was receiving 144 mg of T-1249 once daily (in cohort 9); starting on day 10 of treatment, this patient experienced several large (10–15 cm) macular lesions that were characterized by swelling, erythema, and tenderness at injection sites and were concurrent with chills and fever. The patient completed the 14-day treatment period without interruption of T-1249, and the symptoms markedly improved 4 days after the patient's last dose. Although a measurable IgG response against T-1249 was not detected in the first patient, an increase of 32-fold from baseline in T-1249–specific IgG was detected in the latter (see below).

Serum antibody analysis. Forty-three percent of all patients (49/115) exhibited a preexisting IgG antibody titer that was cross-reactive to T-1249. Paired (baseline and day-14) serum antibody results were obtained for 114 patients (99%); paired results for 14 patients (12%) demonstrated an increase ($\geq$8-fold; see Subjects, Materials, and Methods) from baseline measurements in anti–T-1249 IgG response. Three of these patients had preexisting antibodies reactive with T-1249, and the other 11 developed a de novo response. This antibody response appeared to be specific to T-1249, since the anti-enfuvirtide-reactive antibody titer for these samples remained unchanged (data not shown). However, the frequency of developing a positive IgG antibody response did not appear to increase with increased daily dose of T-1249.

Several selected treatment-emergent signs and symptoms known to be associated with allergic reactions (e.g., body rash, fever, grade 3 or 4 thrombocytopenia, and neutropenia) were analyzed with respect to the changes in antibody titers. Of the 14 patients who experienced an increase in antibody titers against T-1249 (range, 8–2048-fold), 6 (43%) concurrently experienced a rash and/or fever. Of the 100 patients who did not experience an increase in anti–T-1249 IgG response, 20 (20%) experienced a rash and/or fever ($P = .084$, by Fisher's exact test). Furthermore, an increase in anti–T-1249 IgG response did not appear to be associated with either a diminished antiretroviral response to T-1249 or a higher frequency of viral rebound (data not shown).

DISCUSSION

This 14-day dose-escalation monotherapy study of T-1249, in a heavily pretreated population with advanced HIV-1 disease, has demonstrated very potent dose-dependent antiviral responses. Increases in $CD4^+$ cell counts observed in the higher-dose cohorts also provide indirect evidence that T-1249 elicits antiviral activity.

The decreases in HIV-1 RNA load observed in the higher-dose cohorts were ~2 $\log_{10}$ copies/mL, which are similar to those observed during short-term therapy with the most potent antiretrovirals that are currently available [19]. Moreover, decreases in virus load over 10–14 days were in the same range as those in studies in which several antiretroviral agents were simultaneously introduced [20]. These observations suggest that the experimental model using short-term monotherapy and multiple measurements of virus load may not be able to detect reductions in HIV-1 RNA loads beyond 99% of the virus load at baseline. This may be explained by the fact that the virus being measured in plasma at a particular time is derived from different reservoirs, each representing a population with varying half-lives [19, 21]. Thus, by use of this model, the maximum decrease in HIV-1 RNA load may never exceed ~2 $\log_{10}$ copies/mL, and, therefore, this model may not be able to further discriminate the antiretroviral activity (i.e., decrease in HIV-1 RNA load) elicited by higher doses. That the 2 highest doses of T-1249 tested reached the maximum activity of this model suggests that further testing of higher doses would not

Table 2. Phenotypes for virus isolates demonstrating genotypic changes.

Patient	Baseline HIV-1 RNA load, $\log_{10}$ copies/mL	Nadir response, $\log_{10}$ copies/mL[a]	HIV-1 RNA response at day 14, $\log_{10}$ copies/mL	Genotypic change at day 14[b]	Fold change in T-1249 IC_{50} (R5/X4)[c]	Fold change in ENF IC_{50} (R5/X4)[c]
A	6.00	−1.21	−0.43	V38V/E; Q40Q/K	25.7 (R5)	122.4 (R5)
B	5.89	−0.84	−0.84	V38V/E	8.3 (R5)	44.0 (R5)
C	5.30	−1.53	−0.89	V38V/E	14.2 (X4)	41.0 (X4)
D	5.26	−2.12	−2.12	Q40K	5.9 (R5)	81.3 (R5)
E	5.51	−2.01	−1.24	Q40Q/K	3.2 (R5)	111.6 (R5)

[a] Maximum decrease in $\log_{10}$ HIV-1 RNA copies/mL over the 14-day treatment period. ENF, enfuvirtide.
[b] Treatment-emergent genotypic changes in gp41 aa 36–45.
[c] R5 and X4 refer to the usage of the CCR5 and/or CXCR4 coreceptor. For dual-tropic viruses, the maximum IC_{50} value of X4 and R5 is reported.

have identified any additional antiretroviral activity. Nevertheless, that doses of 144 and 192 mg/day achieved very potent antiretroviral responses in fusion inhibitor–naive patients suggests that appropriate doses given once daily can provide exposures resulting in effective pharmacodynamic properties.

T-1249 was well tolerated over the 14-day treatment period, and a maximum tolerated dose was not achieved. Overall, there was no apparent dose-response relationship for AEs, with the exception of ISRs. Although these were experienced by most patients, most ISRs were mild in severity. For cohorts 7–10, the incidence of ISRs increased with increased daily dose, possibly because of the greater number of injections required as the dose increased. Although the highest concentrated formulation used in this study was 48 mg/mL, forthcoming studies will treat patients with a formulation containing ⩾100 mg/mL, reducing the number of required injections for patients receiving T-1249.

Unlike enfuvirtide, whose sequence replicates part of the consensus sequence of the HR2 region of HIV-1 gp41, T-1249 is composed of sequences derived from HIV-1, HIV-2, and SIV. Thus, administration of T-1249 results in challenge with a neoantigen, with the potential to trigger immune mechanisms. Serum antibody determinations in nonclinical studies have revealed that nearly all primates treated with T-1249 develop antibodies to the compound within 14 days (authors' unpublished data); however, no clear response was apparent between the magnitude of antibody response and T-1249 exposure or toxicity. In the present study, some patients experienced an anti–T-1249 antibody response at baseline (before the first dose of T-1249). Given that T-1249 shares some sequence homology with HIV-1 gp41, this cross-reaction is presumably a result of exposure to the envelope gp41 during infection with HIV-1.

Table 3. Most frequently reported (⩾10%) treatment-emergent adverse events (AEs).

AE[a]	No. (%) of patients (N = 115)
Headache	16 (14)
Pyrexia	16 (14)
Rash	15 (13)
Maculo-papular	6 (5)
Dermatitis	5 (4)
Papular	2 (2)
Erythematous	1 (<1)
Urticaria	1 (<1)
Lymphadenopathy	11 (10)
Oral candidiasis	11 (10)

[a] All AEs, excluding injection-site reactions, unless they met the definition of a severe AE.

The presentation of a patient in cohort 6 with fairly typical symptoms of drug hypersensitivity further highlighted the potential for allergic-like signs/symptoms. Two patients in the present study had AEs that were suggestive of an allergic reaction to T-1249. The patient in cohort 6 with a presumed drug-hypersensitivity reaction did not have an anti–T-1249 antibody response, whereas the other patient who presented with fever and progressively worsening erythema with edema at the injection sites had a new IgG response after treatment with T-1249 (32-fold increase from baseline in T-1249–specific IgG). A minority (12%) of patients developed or increased the titer of anti–T-1249 IgG antibodies, suggesting that specific antibody responses to T-1249 can be mounted in humans. The occurrences of rash and/or fever were compared among patients who did and did not have increases in anti–T-1249 antibody. Although there was a trend suggesting that these AEs may have occurred more commonly in patients who developed IgG antibodies to T-1249, the conclusions are limited because of the small sample size. Furthermore, given the uncontrolled study design, it is not possible to conclusively demonstrate that the events were due to T-1249. Chronic-dosing studies will be able to better define the clinical significance of the antibody response.

Studies performed in vitro and in patients exposed to enfuvirtide have demonstrated that mutations associated with resis-

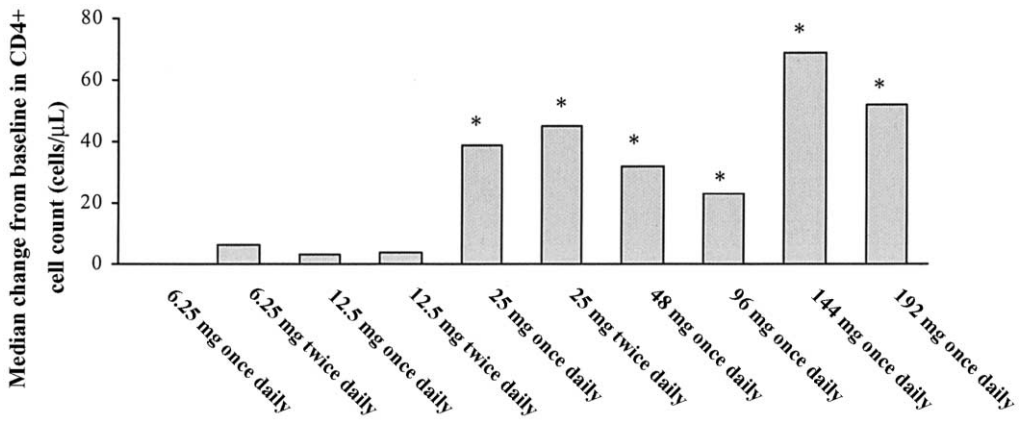

Figure 3. $CD4^+$ cell counts (median change from baseline, at day 14) among the dose cohorts. $*P < .05$ (Wilcoxon signed-rank test).

tance to enfuvirtide have been observed predominantly in the gp41 region, between 36 and 45 aa [11]. In a preliminary exploration of the T-1249 resistance profile, genotypic changes from baseline associated with reduced susceptibility to T-1249 were identified in the HR1 region after treatment, suggesting that these mutations (V38E and Q40K) were selected by T-1249 in vivo. Further analyses of sequence changes outside of the 36-45-aa region of HR1 that were not clearly associated with changes in susceptibility or viral rebound are ongoing. Of importance, all virus isolates with resistance to T-1249 also had decreases in susceptibility to enfuvirtide, suggesting that, whereas most enfuvirtide-resistant isolates retained sensitivity to T-1249 [11], the reverse is not likely to be true. The T-1249 resistance profile will continue to be better characterized as a larger number of patients receive T-1249 in chronic-dosing studies.

In conclusion, a novel HIV entry inhibitor, T-1249, elicited very potent antiretroviral activity and was generally safe and well tolerated over 14 days, in HIV-1 infected patients who had extensive pretreatment experience with antiretroviral medications. Analyses of efficacy demonstrated dose-dependent antiretroviral activity, with the greatest antiretroviral response resulting from the highest daily doses (144 and 192 mg). Ongoing studies are investigating the safety of T-1249 during chronic dosing and the activity of T-1249 in enfuvirtide-experienced patients whose virus has reduced susceptibility to enfuvirtide [12]. These studies will help define the role of T-1249 for the treatment of HIV-infected individuals.

Acknowledgments

We would like to extend our thanks to Janice Gleavy for the original study planning and supervision of the study conduct for cohorts 1–6. We thank the following Trimeris personnel: Emily McFalls, for drug-safety oversight; Prakash Sista, for help with virological testing; and Brian Baker, for serum-antibody method development and sample analysis. Additionally, we rec-

Table 4. Summary of T-1249 injection site reactions (ISRs) for cohorts 7–10.

	Dose cohort (no. of persons in intent-to-treat [ITT] population), dose level				
Reaction	Cohort 7 (N = 14), 48 mg/day	Cohort 8 (N = 13), 96 mg/day	Cohort 9 (N = 12), 144 mg/day	Cohort 10 (N = 13), 192 mg/day	Cohorts 7–10, all patients
No. of injections per daily dose	1	2	3	4	
At least 1 ISR	8 (57)	10 (77)	11 (92)	12 (92)	41 (79)
No. of ISRs reported	17	28	28	36	109
Symptom					
Erythema	5 (36)	6 (46)	8 (67)	7 (54)	26 (50)
Subcutaneous induration	3 (21)	4 (31)	8 (67)	7 (54)	22 (42)
Pruritus	2 (14)	2 (15)	3 (25)	3 (23)	10 (19)
Subdermal nodules/cysts	1 (7)	2 (15)	5 (42)	5 (38)	13 (25)
Ecchymosis	1 (7)	2 (15)	3 (25)	7 (54)	13 (25)

NOTE. Data are no. (%) of patients, unless otherwise noted. Each patient is counted once per sign or symptom. Percentages are based on the number of ITT patients in that cohort.

ognize Tina Korich at Virologic for help with sample processing. For their work and dedication, we give a special "thank you" to all study-site personnel, including the following study investigators and coordinators: Linh Ngo, Susan Pederson, Valery Hughes, Megan McDaniels, Jane Norris, Ingrid Hansen-Barthel, Glenda Black-Sprouse, Kalliope Halkias, Kathy Habeeb, Beverly Putnam, John Gourely, Ann Tanaka, Anne Howely, Ben Barnett, Nesli Basgoz, Daniel Kuritzkes, Fred Valentine, David Wheeler, and Jeffrey Nadler. Lastly, we are greatly indebted to all study participants.

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