

## CONCISE COMMUNICATION

## Safety, Tolerability, and Pharmacokinetic Effects of Thalidomide in Patients Infected with Human Immunodeficiency Virus: AIDS Clinical Trials Group 267

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Thalidomide is used to treat human immunodeficiency virus (HIV)–associated conditions, including aphthous ulcers and wasting syndrome. The safety, tolerability, and pharmacokinetics of a formulation of thalidomide with improved bioavailability in HIV-infected persons was examined in a placebo-controlled, dose-escalating phase 1 study. Subjects with CD4 cell counts of 200–500 cells/mm<sup>3</sup> were enrolled and randomized 3:1 in groups of 12 to receive 50, 100, or 150 mg of thalidomide or matching placebo. Two subjects who received 150 mg of drug and 2 subjects assigned placebo experienced dose-limiting toxicity. Concentrations of thalidomide in the blood increased with escalating dose, but the time to maximum concentration and clearance did not differ across dose cohorts. Previous suggestions of autoinduction of drug metabolism were not confirmed by this study. At the doses studied, thalidomide was tolerated well and had linear pharmacokinetics.

Thalidomide ( $\alpha$ -N-phthalimidoglutaride) is a major therapy for severe refractory human immunodeficiency virus (HIV)–associated aphthous ulcers and is often used to treat other complications of HIV disease, including wasting syndrome, diarrhea, prurigo nodularis, and Kaposi's sarcoma [1–7]. However, the safety, tolerability, and pharmacokinetics of thalidomide in HIV-infected persons have not been examined fully. Short-term studies have demonstrated a relatively high rate of toxicity to thalidomide at empirically derived doses among persons with HIV infection—particularly among those with low CD4 cell counts [8].

To date, evaluation of the pharmacokinetics of the drug in HIV-infected persons has been restricted primarily to single-dose stud-

ies that do not provide data on the pharmacokinetics of the most recent and widely used formulation of the drug (Celgene) under multiple dose conditions in HIV-infected patients [9, 10]. Furthermore, some concern exists as to whether thalidomide may induce its own metabolism following chronic dosing [11]. To increase understanding of the safety, tolerability, and pharmacokinetics of thalidomide, we conducted a phase 1, double-blind, placebo-controlled, dose escalation study of oral thalidomide in HIV-infected patients without AIDS.

### Methods

**Study population.** Thirty-nine subjects were enrolled at 7 sites in the United States. Subjects were  $\geq 18$  years old, had documented HIV infection, had CD4 cell counts of 200–500 cells/mm<sup>3</sup>, and received stable antiretroviral therapy or no HIV therapy for a minimum of 60 days prior to enrollment. Women were enrolled if they were amenorrheic or had been surgically sterilized previously. Patients were excluded for the following reasons: history of bilateral peripheral neuropathy more severe than toxicity grade 1 (National Institute of Allergy and Infectious Disease criteria), ongoing short-term therapy for opportunistic infections, diagnosis of active tuberculosis within 3 months prior to entry, systemic malignancy requiring chemotherapy, treatment with other putative immunomodulators within 2 weeks before study entry, or current therapy with a central nervous system active agent that could not be stopped in the event of an adverse experience during the study.

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Institutional review boards of each medical center approved the study. All subjects gave written informed consent.

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**Treatment regimens.** This study was a double-blind, placebo-controlled, dose escalation study of oral thalidomide (Celgene). Three dosage cohorts (50, 100, and 300 mg daily) were originally planned and were to be successively accrued, with a maximum of 12 subjects enrolled per cohort until the maximum tolerated dose was achieved. Within each dosage cohort, subjects were randomized to thalidomide versus placebo for 8 weeks in permuted blocks of 4, with 3 subjects receiving active drug for each subject assigned placebo. The occurrence of  $\geq 3$  dose-limiting toxicities in a dosage cohort mandated discontinuation of that cohort, and the previous dosage cohort was declared the maximal tolerated dose. Dose-limiting toxicity was defined as grade 2 or greater peripheral neuropathy, grade 3 or greater rash or fever, or somnolence unacceptable to the subjects for  $\geq 72$  h.

A 100-mg cohort was added after the study team learned that 3 subjects assigned to thalidomide experienced dose-limiting toxicity in the 150-mg cohort. Rather than declare 50 mg the maximally tolerated dose, the study was amended to include a new dosage cohort of 100 mg daily. Subsequent to completion of enrollment into the 100-mg cohort, it was discovered that 1 of the dose-limiting toxicities that occurred in the 150-mg dose cohort was experienced by a subject receiving placebo and not active drug. The 100-mg cohort enrolled fully, and the study was completed.

**Evaluation of patients and follow-up.** After screening and baseline procedures, subjects were evaluated for new signs, symptoms, diagnoses, toxicities, and medication changes, as well as laboratory evaluations, 1, 2, 4, 6, 8, and 10 weeks after study entry. Subjects were admitted to general clinical research units for pharmacokinetics at entry (first dose of study medication), at week 2, and at week 8 (last dose of study medication). At weeks 2 and 8, subjects were instructed to not take the previous day's dose of study medication until after the first blood sampling on the mornings of pharmacokinetic sessions.

**Pharmacokinetics.** Plasma thalidomide levels were measured over 24 h at entry and at weeks 2 and 8 for each of the 3 cohorts. Sampling was done before dosing and at 0.5, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, and 24 h after dosing. Blood was collected in heparinized Vacutainer tubes (Becton Dickinson) and centrifuged. Plasma was harvested and stored in vials at  $-70^{\circ}\text{C}$ . Samples were analyzed by use of a validated high-performance liquid chromatography method based on a previously published method [12]. Storage stability and freeze-thaw stability studies indicate that thalidomide concentration changes of  $-6.3\%$  to  $5.8\%$  can be expected for low- and high-quality assurance controls for over 24 h at room temperature and below 1% for freeze thaw cycles.

**Statistical analysis.** All the *P* values reported are from 2-sided tests, unless otherwise specified. Three basic statistical tests were performed. We used Fisher's exact test to test the association between categorical variables and treatment assignment or toxicity grade and the Kruskal-Wallis test (or Wilcoxon rank sum test) to test whether the distribution of a continuous variable was the same among treatment groups versus a shift alternative. We used a Wilcoxon signed rank test to determine whether the median of a continuous variable was the same among the treatment groups (to determine whether the median of a continuous variable equals zero within the group).

**Pharmacokinetic analysis.** Noncompartmental pharmacokinetic analysis for the disposition of plasma thalidomide level was determined with WINNONLIN computer software (Pharsight). The peak concentration ( $C_{\text{max}}$ ) and time to peak concentration ( $T_{\text{max}}$ ) for tha-

lidomide were taken as the maximum measured concentration. The area under the concentration-time curve (AUC) for thalidomide was calculated by using the linear trapezoidal rule for increasing plasma concentrations and the log trapezoidal rule for decreasing concentrations. Extrapolation of AUC to infinity ( $\text{AUC}_{0-\infty}$ ) was performed by dividing the last observed data point on the AUC by the terminal disposition rate constant ( $\lambda_z$ ), which was obtained by exponential regression of at least the last 3 points. The apparent total body clearance as a function of bioavailability ( $Cl/F$ ) was calculated by the following equation:  $Cl/F = \text{dose}/\text{AUC}_{0-\infty}$ . The apparent volume of distribution ( $V\beta/F$ ) was also calculated by using noncompartmental methods ( $[Cl/F]/\lambda_z$ ). The half-life ( $t_{1/2}$ ) was determined by dividing  $0.693 (\ln 2)$  by  $\lambda_z$ . *P* values of Kruskal-Wallis tests of treatment difference (excluding the placebo group from the analysis) are given for each parameter at weeks 0, 2, and 8.

**Pharmacodynamic analysis.** We used 2 methods to evaluate the association between pharmacokinetics parameters and toxicity. First, for each subject assigned to a thalidomide group, we calculated the mean value of pharmacokinetic parameter estimates at the evaluation times prior to dose modification (AUC,  $C_{\text{max}}$ , and  $t_{1/2}$ ). Then we compared the AUC,  $C_{\text{max}}$ , and  $t_{1/2}$  values between patients with versus those without a greater than grade 3 toxicity or dose-limiting toxicity by use of a Wilcoxon rank sum test. Second, for each subject, by using the same pharmacokinetics parameter estimate (AUC,  $C_{\text{max}}$ , and  $t_{1/2}$ ) as described above, we categorized each subject's mean parameter value as either above or below the group median of all subjects who took thalidomide and then tested for an association between pharmacokinetics parameter above or below the median and greatest toxicity grade experienced on study.

## Results

**Study population.** From May 1995 to September 1998, 39 subjects were enrolled. Two subjects were enrolled prior to the availability of a new formulation of thalidomide. Another subject enrolled to the 150-mg dosage cohort discontinued study medication within 2 weeks of study entry without dose-limiting toxicity. These 3 subjects were not included in the final analyses. The 50- and 150-mg dosage cohorts accrued fully, with 12 subjects in each cohort. The 100-mg cohort was added (see Methods) and enrolled 12 subjects, and the study was completed. For the 36 subjects, median follow-up was 16 weeks. Median time receiving study treatment was 8 weeks. Table 1 lists the baseline characteristics of the 36 subjects in the analyses.

**Safety and tolerability.** Dose-limiting toxicities were experienced by 2 subjects receiving 150 mg of thalidomide and by 2 assigned placebo. Of these subjects, both subjects receiving active drug reported somnolence at grades 2 and 3, respectively. Of the subjects randomized to placebo, 1 reported grade 3 somnolence and the other reported grade 2 peripheral neuropathy. A maximally tolerated dose was not reached, and there was no statistical difference among the treatment groups in terms of the proportion of subjects who experienced a dose-limiting toxicity ( $P = .295$ ). An additional 3 subjects reduced study medication dose, temporarily interrupted study drug, or prematurely discontinued

**Table 1.** Baseline characteristics of study population, by treatment group.

Characteristic	Total	Placebo	Thalidomide		
			50 mg	100 mg	150 mg
No. of patients	36	9	9	9	9
Age, median years	37	37	37	41	33
Male, %	86	78	89	89	89
White, %	56	44	56	78	44
Injection drug users, %	22	11	0	33	44
CD4 cell count, median cells/mm <sup>3</sup>	338	350	290	326	399
CD8 cell count, median cells/mm <sup>3</sup>	923	1025	815	1164	778
HIV RNA level, median copies/mL <sup>a</sup>	4812	15,518	32,961	1071	1207
HIV RNA level, median log <sub>10</sub> copies <sup>b</sup>	3.64	4.19	4.52	2.89	3.03
No. of agents in antiretroviral therapy, no. of subjects					
None	NA	3	4	1	2
1	NA	3	5	0	0
2	NA	2	0	4	2
≥3	NA	1	0	4	5

NOTE. HIV, human immunodeficiency virus; NA, not applicable.  
<sup>a</sup> *P* = .0194.  
<sup>b</sup> *P* = .0125.

study treatment for reasons other than development of dose-limiting toxicity. One of these subjects developed grade 3 thrombocytopenia while receiving 150 mg of thalidomide but, after a 1-week hiatus in therapy, resumed the original dose without incident. Two subjects, 1 assigned to receive 100 mg of thalidomide and the other placebo, prematurely discontinued study medication at their request without report of toxicity.

The occurrence of grade 3 or higher clinical or laboratory adverse events was no different between those randomized to receive thalidomide or placebo. Two subjects in the placebo group, 2 in the 50-mg thalidomide arm, 1 in the 100-mg thalidomide arm, and 3 in the 150-mg thalidomide arm had grade 3 or worse laboratory abnormalities (*P* = .944). Three subjects in the placebo group (33%) and 1 subject in each of the 3 thalidomide dose regimens (11%) had a grade 3 sign or symptom (*P* = .976, 1-sided). These signs and symptoms included fatigue, discomfort, and edema. There were no grade 4 clinical adverse events. There was no significant difference in the median change in plasma HIV-1 RNA levels within any of the dose cohorts or between thalidomide dosage arms and placebo at any time during the study.

**Pharmacokinetics of thalidomide.** Thalidomide pharmacokinetics were linear over the range of doses evaluated, with no apparent difference in *Cl/F* values among dose cohorts (table 2). AUC did not increase significantly over time in any of the cohorts but increased significantly across cohorts as the dose increased at baseline (*P* = .0003) and week 2 (*P* = .005). At week 8, there was a trend toward increasing AUC across the cohorts (*P* = .07),

but only 5 subjects in the 150-mg cohort underwent intensive sampling. *Cl/F* declined significantly between weeks 0, 2, and 8 in the first cohort (*P* = .042) but not in the other 2 cohorts.

Neither the *Vβ/F* nor the *t*<sub>1/2</sub> value differed across dose or time. Thalidomide was absorbed rapidly, with a mean *T*<sub>max</sub> of 2.36–2.71 h with no impact of dose or time (figure 1).

In comparisons of median AUC, *C*<sub>max</sub>, and *t*<sub>1/2</sub> values between thalidomide-receiving subjects with and without grade 3 or worse adverse events or dose-limiting toxicities, there were no differences in pharmacokinetic parameters. Categorization of each subject's AUC, *C*<sub>max</sub>, and *t*<sub>1/2</sub> data as above or below the median of all subjects receiving thalidomide failed to predict toxicity.

**Discussion**

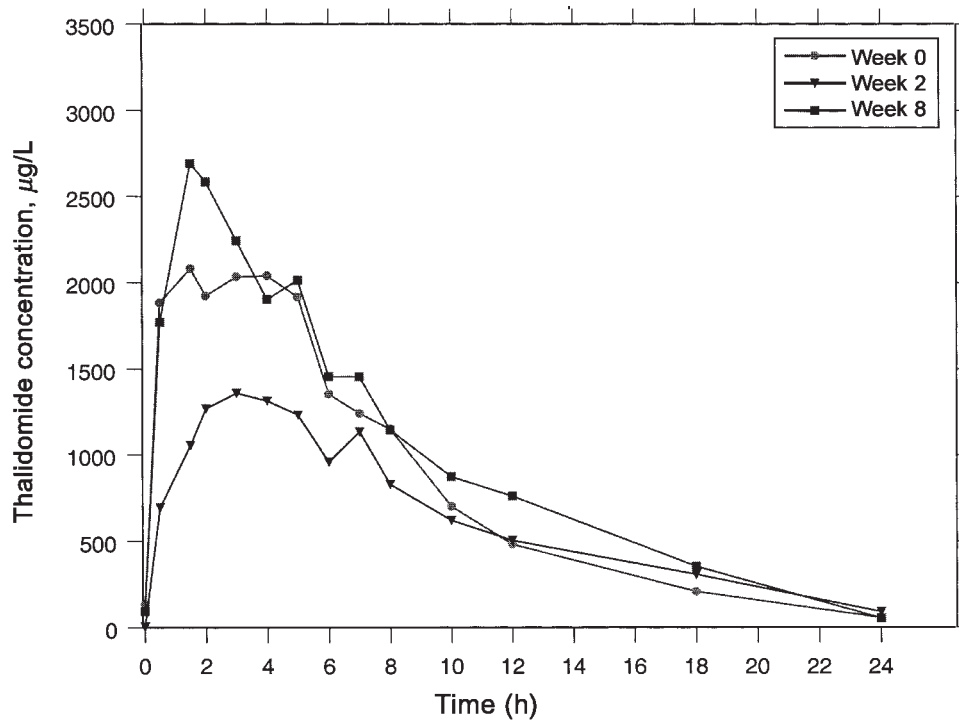
In this study, thalidomide at doses up to 150 mg daily was well tolerated. The incidence of clinical and laboratory adverse events

**Table 2.** Thalidomide pharmacokinetic parameters.

Dose cohort, week (no. of patients)	<i>C</i> <sub>max</sub> , μg/L	<i>T</i> <sub>max</sub> , h	AUC <sub>0-∞</sub> , μg × h/L	<i>Cl/F</i> , L/h/kg	<i>t</i> <sub>1/2</sub> , h	<i>Vβ/F</i> , L/kg
50 mg						
Week 0 (8)						
Mean	811.25	2.31	5779.79	0.12	4.20	0.72
SD	202.86	1.53	1375.67	0.02	0.75	0.19
Week 2 (8)						
Mean	918.38	2.07	6779.74	0.10	6.00	0.82
SD	375.82	.82	2695.45	0.04	2.07	0.19
Week 8 (9)						
Mean	1094.89	2.71	8779.03	0.08	7.11	0.81
SD	459.94	2.08	3209.15	0.02	2.43	0.31
<i>P</i> <sup>a</sup>	.497		.079	.042		
100 mg						
Week 0 (8)						
Mean	1211.50	2.94	12,436.09	0.12	7.40	1.14
SD	253.76	1.27	4080.10	0.03	5.69	0.64
Week 2 (9)						
Mean	1512.67	2.02	9887.49	0.25	4.46	1.50
SD	1115.59	0.96	7507.47	0.20	1.69	1.04
Week 8 (8)						
Mean	1433.0	2.21	11,391.02	0.13	6.35	1.06
SD	232.47	0.92	3227.82	0.05	2.33	0.29
<i>P</i> <sup>a</sup>	.269		.274	.267		
150 mg						
Week 0 (8)						
Mean	2803.63	2.89	23,694.64	0.14	5.94	1.13
SD	2463.48	2.09	19,415.11	0.07	2.33	0.53
Week 2 (6)						
Mean	1684.67	3.25	18,257.98	0.14	7.34	1.17
SD	633.74	1.94	7589.88	0.05	3.03	0.63
Week 5 (5)						
Mean	3229.60	2.40	20,999.68	0.16	5.72	1.43
SD	3334.57	2.04	17,532.77	0.11	1.92	1.19
<i>P</i> <sup>a</sup>	.703		.932	.979		

NOTE. AUC<sub>0-∞</sub>, area under the concentration-time curve to infinity; *Cl/F*, apparent total body clearance as a function of bioavailability; *C*<sub>max</sub>, peak concentration; *t*<sub>1/2</sub>, half-life; *T*<sub>max</sub>, time to peak concentration; *Vβ/F*, volume of distribution with respect to bioavailability.

<sup>a</sup> Comparison of weeks 0, 2, and 8.



**Figure 1.** Plasma concentrations of thalidomide over 24 h following administration of 150 mg (cohort II) at weeks 0, 2, and 8

was no greater among subjects assigned thalidomide, compared with placebo. Previous studies have described greater intolerance to thalidomide among HIV-infected patients [1–3, 8]. A report on the safety of thalidomide among 45 HIV-infected subjects who received doses of 200 mg daily for 14–21 days frequently found treatment-limiting toxicities, especially cutaneous and febrile reactions (occurring in 46% of the subjects) [8]. Importantly, in this study, the development of adverse effects was inversely related to CD4 cell count. Likewise, in an AIDS Clinical Trials Group study of thalidomide for treatment of oroesophageal aphthae among subjects with a median CD4 cell count of 23 cells/mm<sup>3</sup>, a much higher rate of adverse effects was observed [1]. Furthermore, in that study, plasma HIV RNA levels increased following thalidomide treatment. However, we did not detect significant increases in virus load in this relatively small and brief study of thalidomide.

The lower rate of adverse events observed in our study may be due to the relatively high CD4 cell count of the cohort. In addition, lower doses of thalidomide were used in this dose-escalating study than in previous treatment trials. Of note, the formulation of thalidomide used in this study had better bioavailability than other formulations of the drug, as evidenced by the relatively high  $C_{max}$  and rapid  $T_{max}$  measured in this study. We found that the median  $C_{max}$  following a single 150-mg dose of thalidomide (1453 µg/L) was more than double the  $C_{max}$  observed by Verbon et al. [13] following administration of 400 mg of an earlier formulation of the drug to healthy volunteers. Although a maximally tolerated dose was not identified, other studies have documented poor tol-

erability of doses of the drug beyond 200–300 mg [1–3, 8]. Furthermore, the 8-week duration of thalidomide treatment may have limited our ability to detect long-term adverse effects of the drug, such as peripheral neuropathy.

Thalidomide pharmacokinetics were linear at all doses studied. In addition, the lack of change in  $Cl/F$  for most doses with time, suggests a lack of saturation or autoinduction of thalidomide metabolism, with no impact of duration of treatment on the apparent clearance of the drug. Therefore, despite reports suggesting autoinduction [12], this was not observed in this present study. Results from this investigation are comparable to those in 2 previous studies of chronic dosing. Aweeka et al. [14] reported apparent clearance values averaging 0.14 and 0.12 L/h/kg following 1 and 4 weeks of treatment, respectively, in HIV-infected patients with oral aphthous ulcers, and Trapnell et al. [15] reported values of 0.10 and 0.08 L/h/kg in healthy women at baseline and after 21 days of thalidomide administration.

Thalidomide is beneficial in the treatment of a number of complications of HIV infection. In this study, we demonstrate that thalidomide at doses as high as 150 mg/day is safe and well tolerated and characterized the pharmacokinetic parameters of the drug. These findings should assist in the application of thalidomide for clinical and research purposes.

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