Safety, Pharmacokinetics, and Antiviral Activity of HGS004, a Novel Fully Human IgG4 Monoclonal Antibody against CCR5, in HIV-1–Infected Patients

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Background. HGS004 is a fully human immunoglobulin (Ig) G4 monoclonal antibody against CC chemokine receptor 5 (CCR5) with robust in vitro activity against a diverse panel of CCR5-tropic human immunodeficiency virus type 1 (HIV-1) isolates.

Methods. A single-blind, randomized, placebo-controlled study was conducted in patients infected with CCR5-tropic HIV-1 to evaluate the safety, pharmacokinetics, and antiviral activity of HGS004. Sixty-three subjects were randomized into 5 dose cohorts (0.4, 2, 8, 20, and 40 mg/kg) and received a single intravenous dose of HGS004 or placebo.

Results. HGS004 was well tolerated, and no dose-limiting toxicities were observed. Pharmacokinetics were nonlinear across the 0.4–40-mg/kg dose range, with dose-proportional increases in maximum concentration, although the area under the curve increased more than proportionally to dose. High levels of receptor occupancy were observed for up to 28 days in the higher-dose cohorts. Plasma HIV-1 RNA reductions of >1 $\log_{10}$ at day 14 were observed in 14 (54%) of 26 subjects in the 8-, 20-, and 40-mg/kg cohorts. In the 40-mg/kg cohort, 4 of 10 subjects had a >1 $\log_{10}$ HIV-1 RNA reduction at day 28. Drug concentrations relative to isolate sensitivity (the ratio of the concentration at day 14 to IC_{90}) predicted antiviral response on day 14.

Conclusions. HGS004 is safe and well tolerated and demonstrates meaningful antiviral activity when administered to patients infected with CCR5-tropic HIV-1.

The availability of highly active antiretroviral therapy has markedly improved the outcomes for patients with HIV-1 infection. The success of current therapies is limited, however, by the emergence of drug-resistant viruses, the need for sustained adherence to complex regimens, and the potential for toxic side effects. Entry inhibitors represent an exciting class of new agents, because they can block HIV-1 infection at the earliest stages of the virus life cycle [1–4]. CCR5 is a chemokine receptor on the cell surface that, together with CD4, mediates the binding of the HIV-1 envelope and promotes viral entry into the cell. Natural chemokine ligands for CCR5 include macrophage inflammatory protein (MIP)–1α and MIP-1β, RANTES, and monocyte chemotactic protein–2 [5–8]. Small-molecule inhibitors of CCR5 have shown excellent antiviral activity when administered as a single agent in 10-day clinical trials [9, 10]. Longer-term safety and efficacy data for vicriviroc has recently been reported [11], as have phase 3 results for maraviroc, leading to the approval of this agent when used in combination with other classes of antiretroviral agents in treatment-experienced patients [12].

HGS004 is a fully human IgG4 monoclonal antibody that specifically binds to the second extracellular loop of CCR5, thereby inhibiting HIV envelope–dependent cell-cell fusion and blocking viral entry [13]. This antibody is also a potent inhibitor of chemokine (MIP-1α,

Received 14 June 2007; accepted 7 September 2007; electronically published 11 February 2008.

Potential conflicts of interest: G.M.S., L.A.N., W.C., C.C., and J.Z. were employed full time by Human Genome Sciences at the time the study was conducted. All other authors report no potential conflicts.

Financial support: Human Genome Sciences. Statistical, pharmacokinetic, and other analyses were performed by Human Genome Sciences.

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The Journal of Infectious Diseases 2008; 197:721–7

0022-1899/2008/19705-0017$15.00
DOI: 10.1086/527327

MIP-β, and RANTES) binding to the receptor. Importantly, HGS004 does not induce signaling or mediate antibody-dependent, cell-mediated cytotoxicity in human cells [13]. Furthermore, in vitro studies with currently approved agents representing each of the antiretroviral drug classes—nucleoside reverse-transcriptase inhibitors (zidovudine and lamivudine), nonnucleoside reverse-transcriptase inhibitors (efavirenz), protease inhibitors (indinavir), and fusion inhibitors (enfuvirtide)—demonstrated that HGS004 acts synergistically with all currently approved classes of antiretroviral agents [14, 15]. HGS101 is an affinity-matured derivative of HGS004 currently in preclinical development; it is 5–10-fold more potent in blocking HIV-1 entry but retains other characteristics of HGS004. Long-term coculture of clinical isolates in vitro for >24 weeks in the presence of HGS004 or HGS101 failed to result in the emergence of viruses with increased IC_{50} values, suggesting that it may be difficult for viruses to develop resistance to these competitive inhibitors of CCR5 [15].

Here, we report the results of a phase 1 clinical study in patients with HIV-1 infection. The primary objective of the study was to evaluate the safety and tolerability of escalating doses of HGS004 administered as a single intravenous infusion. The secondary objectives were to describe the pharmacokinetics and pharmacodynamics (changes in CD4 cell counts and reductions in HIV-1 RNA levels) of HGS004.

METHODS

Study design. This was a dose-escalation, randomized, single-blind, placebo-controlled, multicenter study. The study was approved by the institutional review boards at each site, and subjects provided written informed consent. Inclusion criteria required documented evidence of HIV-1 infection; subjects who were either naive to previous antiretroviral therapy or, if treatment experienced, had not received any antiretroviral therapy in the 8 weeks before screening; and HIV-1 isolates that were CCR5 tropic by the PhenoSense Entry assay (Monogram Biosciences). Eligible patients had CD4 cell counts >250 cells/μL and plasma HIV-1 RNA levels >5000 copies/mL. Subjects coinfected with hepatitis C or hepatitis B viruses were excluded. Five dose levels were assessed: 0.4, 2, 8, 20, and 40 mg/kg. For each dose level, subjects were randomized to receive either placebo (2 subjects) or active drug (8 subjects), administered as a single intravenous infusion on day 0, and were then followed up for 56 days. Safety data were reviewed by an internal safety monitoring board to enable dose escalation.

Study agent. HGS004 is a recombinant, fully human, IgG4 monoclonal antibody derived from XenoMice (Abgenix) that binds CCR5 with high affinity and was selected on the basis of anti-HIV potency [13]. HGS101 is derived from HGS004 as an affinity-matured (using phage-display technology) second-generation compound with greater antiviral potency. HGS004 and HGS101 are expressed in the NS0 mouse myeloma cell line, secreted into culture medium, and purified by a series of chromatography and filtration steps. HGS004 and placebo were supplied as a lyophilized formulation and stored in sterile, single-use vials. For intravenous administration, the study agent was reconstituted, diluted in normal saline, and infused over 2 h.

Safety and laboratory assessments. Evaluation of safety included adverse event monitoring, physical examination, and clinical laboratory assessments (hematology, serum chemistry, and urinalysis). Safety was assessed from baseline before dosing through 56 days after treatment. Plasma HIV-1 RNA levels and CD4 cell counts were measured on days 0, 1, 2, 4, 7, 14, 21, 28, 42, and 56. Samples were collected to assess HIV-1 isolate tropism (CCR5 tropic, CXCR4 tropic, or dual/mixed [i.e., CXCR4-CCR5]) and isolate susceptibility (IC_{50} and IC_{90}) to HGS004 and HGS101 by use of the PhenoSense Entry assay [11, 12]. The development of anti-HGS004 antibodies was assessed by measuring serum reactivity with HGS004 by ELISA before dosing and up to 56 days after dosing.

Pharmacokinetics. Blood samples for serum HGS004 concentration measurement were collected before dosing; 5 min and 1, 3, and 6 h after completion of infusion on day 0; and on days 1, 2, 4, 7, 14, 21, 28, 42, and 56. Serum HGS004 concentrations were analyzed by a qualified ELISA. Pharmacokinetic analyses were conducted by noncompartmental or compartmental methods using the software package WinNonlin Professional Edition (version 4.1; Pharsight). Because there were no measurable serum HGS004 concentrations reported after day 4 for all subjects in the 0.4-mg/kg cohort, the data were analyzed using a noncompartmental method; only maximum concentration (C_{max}) and area under the curve $(AUC)_{0-last}$ could be evaluated. For the 2-, 8-, 20-, and 40-mg/kg cohorts, a 2-compartment infusion model with first-order elimination from the central compartment was used to fit the pharmacokinetic data. The linearity of the pharmacokinetic data over the dose range evaluated was assessed using 1-way analysis of variance (Prism; version 4.00). A significance level of $\alpha = .05$ was used to assess differences.

Receptor occupancy. Blood samples for the receptor occupancy assay were collected before dosing, 1 h after completion of the infusion on day 0, and on days 1, 7, 14, 28, and 56. To measure relative occupancy of CCR5 on $CD4^+$ T cells from subjects treated with HGS004, a saturation-based flow cytometry blood assay was developed. To establish 100% occupancy, HGS004 was spiked into control wells at a final concentration of 20 μg/mL, because this concentration has been determined to yield maximum staining intensity in the system. Samples of unknown relative occupancy were processed in parallel. All sample wells were washed to remove excess unbound HGS004, followed by incubation with fluorochrome-labeled antibodies in combinations to identify leukocytes (CD45; BD Biosciences), T helper cells (CD4; BD Biosciences), and bound HGS004 (mouse anti–human IgG_4; Southern Biotechnology Associates). Sample analysis was performed on a Becton Dickinson FACSCalibur flow cy-

Table 1. Subject characteristics.

Characteristic	Placebo (n = 13)	HGS004 dose, mg/kg				
		0.4 (n = 8)	2 (n = 13)	8 (n = 9)	20 (n = 10)	40 (n = 10)
Age, mean ± SD, years	40.1 ± 6.4	45.5 ± 3.5	40.4 ± 8.8	39.9 ± 5.6	40.6 ± 6.9	39.6 ± 6.2
Male sex, no. (%)	9 (69)	8 (100)	12 (92)	8 (89)	8 (80)	9 (90)
Treatment naive/experienced, no.	4/9	5/3	8/5	6/3	1/9	3/7
CD4 cell count, mean ± SD, cells/μL	639 ± 276	364 ± 141	465 ± 155	411 ± 135	480 ± 179	336 ± 110
HIV-1 RNA level, mean ± SD, $\log_{10}$ copies/mL	4.3 ± 0.7	4.8 ± 0.7	4.1 ± 0.7	4.7 ± 0.7	4.0 ± 0.5	4.4 ± 0.5

tometer using CellQuest software for data collection. $CD4^+$ T lymphocytes were selected for analysis by using light-scatter analysis and CD45/CD4 staining. Relative CCR5 receptor occupancy was determined by dividing the mean fluorescence intensities of 3 replicates of the human IgG_4 reporter fluorochrome in the unknown samples by the fluorescence mean of 3 replicates of the human IgG_4 reporter fluorochrome in the spiked samples, with the result expressed as a percentage.

Statistical analyses. For safety analyses, the modified intention-to-treat population was used, defined as the subset of all randomized subjects who received study agent. Data on the occurrence of adverse events were analyzed using Fisher's exact test. The Spearman correlation coefficient was used to assess the association between HIV-1 RNA reduction on day 14 and HGS004 concentrations in excess of clinical isolate IC_{90} for individual subjects. A linear regression model was used to reveal the relationship between HIV-1 RNA reduction and the ratio of serum concentrations of HGS004 and isolate IC_{90}. All statistical tests were 2 sided and were performed at a significance level of .05 unless otherwise specified. Because of the exploratory nature of this study, no adjustments for multiple data comparisons were made. All statistical analyses were performed using SAS, R statistical package, Prism, and WinNonlin software.

RESULTS

Subject disposition and patient demographics. A total of 131 subjects were screened and 70 subjects were randomized, but 7 subjects withdrew consent after randomization and before receiving treatment. Therefore, 63 randomized subjects received study agent and were treated in 5 treatment groups. Fifty subjects received HGS004, and 13 received placebo. All subjects completed the study. Data for all subjects were included in the analyses. The demographics of subjects across the treatment groups were well balanced for age, sex, and baseline HIV-1 RNA levels (table 1). The majority of subjects were male (54/63 [86%]), the mean age was 41 years, the mean HIV-1 RNA level was 4.4 $\log_{10}$ copies/mL, and mean CD4 cell counts ranged from 336 to 639 cells/μL. The proportion of treatment-naive subjects varied across treatment groups.

Safety and tolerability. In general, HGS004 was safe and well tolerated. No severe (grade 3–4) adverse events were observed. Most of the adverse events were transient, mild to moderate in severity, and similar in type and severity among placebo and active treatment subjects. Two treatment-related serious adverse events (moderate severity) of infusion-related urticarial rash occurred in the 2-mg/kg cohort. Both subjects were treated with a single dose of diphenhydramine with rapid clinical response, and no recurrence of urticaria was observed during the study duration for either subject. Subsequent subjects were pre-

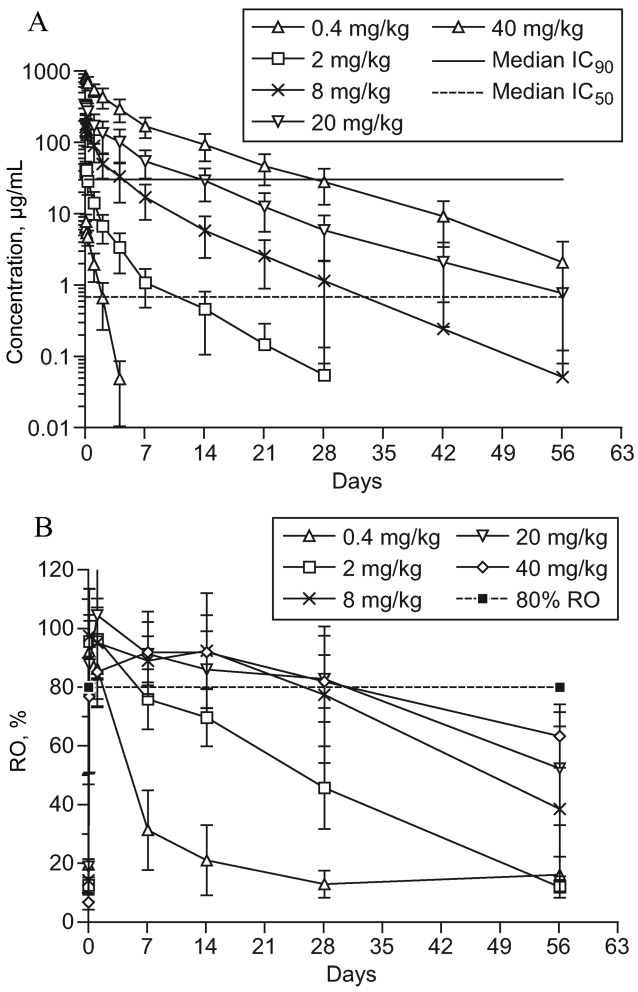

Figure 1. Serum concentration of HGS004 *(A)* and receptor occupancy (RO) of CD4 cells expressing CCR5 in peripheral blood by HGS004 *(B)* in subjects receiving a single intravenous infusion of 0.4, 2, 8, 20, or 40 mg/kg.

Table 2. Pharmacokinetic parameters for the 5 treatment cohorts.

Parameter	HGS004 dose, mg/kg					P[a]
	0.4 (n = 8)	2 (n = 13)	8 (n = 9)	20 (n = 10)	40 (n = 10)	
C_{max}/dose, kg/mL	0.021 ± 0.004	0.020 ± 0.005	0.021 ± 0.006	0.016 ± 0.004	0.021 ± 0.040	.1254
$AUC_{0-\infty}$/dose, kg·day/mL	0.014 ± 0.003	0.029 ± 0.011	0.059 ± 0.024	0.074 ± 0.036	0.111 ± 0.031	<.0001
$t_{1/2,\alpha}$, days	. . .	0.61 ± 0.22	0.79 ± 0.39	0.83 ± 0.84	1.09 ± 0.67	.2931
$t_{1/2,\beta}$, days	. . .	4.73 ± 1.24	5.24 ± 1.87	7.34 ± 2.41	7.94 ± 2.07	.0008
V_{SS}, mL/kg	. . .	108.3 ± 34.7	96.9 ± 32.7	133.1 ± 50.3	89.8 ± 23.9	.0628
CL, mL/day/kg	. . .	38.3 ± 16.1	21.4 ± 14.5	16.9 ± 8.4	9.8 ± 3.0	<.0001
MRT, days	. . .	3.2 ± 1.4	5.2 ± 1.8	8.5 ± 2.0	9.5 ± 2.0	<.0001

NOTE. Data are mean ± SD values and were analyzed using a noncompartmental model. AUC, area under the curve; CL, total body clearance of drug from serum; C_{max}, maximum concentration; MRT, mean residence time; $t_{1/2,\alpha}$, distribution-phase half-life; $t_{1/2,\beta}$, elimination-phase half-life; V_{SS}, volume of distribution at steady state.

[a] P values were determined by 1-way analysis of variance, with a significance level of $\alpha = .05$.

treated with oral diphenhydramine before the infusion. No instances of rash were observed in the additional 6 subjects who were enrolled in the 2-mg/kg cohort or in the higher-dose cohorts. No clinically significant laboratory abnormalities were observed. Adverse events did not appear to be dose related. The most common adverse events among the 50 subjects receiving HGS004 were infusion-site bruising (4/50 [8%]), nasopharyngitis (4/50 [8%]), cough (2/50 [4%]), diarrhea (2/50 [4%]), urticarial (2/50 [4%]), fatigue (2/50 [4%]), headache (2/50 [4%]), otitis externa (2/50 [4%]), and upper respiratory tract infections (2/50 [4%]). Among placebo recipients, chilling (2/13 [15%]) was the most common adverse event.

Pharmacokinetics and receptor occupancy. After a single intravenous infusion of HGS004, drug was detected in serum at all doses evaluated, as shown in figure 1*A*. There was a rapid decline in serum HGS004 concentration in the first 1–2 days, and a more gradual decline over the study duration. Serum HGS004 concentration-time profiles were multiphasic and best fit a 2-compartment open model with first-order elimination from the central compartment. Drug levels in excess of the median IC_{50} of clinical isolates to HGS004 were maintained for ⩾28 days at doses ⩾8 mg/kg (figure 1*A*). However, only the 8-, 20-, and 40-mg/kg doses achieved HGS004 levels in excess of median isolate IC_{90} for significant periods of time. As shown in table 2, the pharmacokinetic data were nonlinear; C_{max} was dose proportional, whereas AUC increased more than proportionally to dose. The mean distribution-phase half-life ($t_{1/2,\alpha}$) was 0.6–1.1 days, and the mean terminal elimination-phase half-life ($t_{1/2,\beta}$) was 4.7–7.9 days. Mean HGS004 clearance after a single intravenous dose ranged from 9.8 to 38.3 mL/kg/day, substantially less than the glomerular filtration rate, indicating that, as expected for this monoclonal antibody, renal excretion is not an important clearance pathway. Overall, HGS004 pharmacokinetic data are nonlinear across the 0.4–40-mg/kg dose range. Elimination of HGS004 appears to be dependent on dose, whereas distribution of HGS004 appears to be independent of dose.

The level of CCR5 saturation (receptor occupancy) by HGS004 on CD4 cells in peripheral blood in the different treatment cohorts during the study is shown in figure 1*B*. In the lower-dose cohorts (0.4 and 2 mg/kg), receptor occupancy levels decreased significantly by day 7. In the higher-dose cohorts (8, 20, and 40 mg/kg), high-level (⩾80%) receptor occupancy was observed up to day 28. In the higher-dose cohorts (20 and 40 mg/kg), significant levels of receptor occupancy were observed up to day 56. No clear correlation was observed between receptor occupancy and serum concentrations of HGS004.

Antiviral activity. Significant reductions in HIV-1 RNA were observed only in the higher-dose cohorts (8, 20, and 40 mg/kg), as shown in figure 2. The dynamics of HIV-1 RNA reductions were characterized by minimal decrease in the first 2 days after drug administration. Consistent with the mechanism of action for an entry inhibitor, a rapid decrease in HIV-1 RNA level was observed starting on day 4, with maximal reductions observed on days 7 and 14 in the 8- and 20-mg/kg cohorts. A rebound in HIV-1 RNA level was observed by day 21 in the majority of subjects, with gradual return to baseline by day 56. In the highest-dose treatment group (40 mg/kg), some subjects showed a continued reduction to day 21, as shown in figure 2*B*. The return to pretreatment levels also occurred later in the 40-mg/kg group. The majority of subjects (83%) in the higher-dose groups (8–40 mg/kg) demonstrated a ⩾0.5 $\log_{10}$ reduction in HIV-1 RNA level on day 14. The proportion of subjects with a ⩾1.0 $\log_{10}$ reduction in HIV-1 RNA level on day 14 was 56%, 60%, and 50% in the 8-, 20-, and 40-mg/kg cohorts, respectively. However, a higher proportion of subjects receiving 40 mg/kg of HGS004 maintained a ⩾1.0 $\log_{10}$ reduction on day 28 (40% in the 40-mg/kg group vs. 10.5% in the 8- and 20-mg/kg groups).

All subjects were monitored on days 0, 28, and 56 for change in isolate susceptibility to HGS004 and for the presence of dual/mixed-tropic (CXCR4/CCR5) or CXCR4-tropic isolates. A dual/mixed virus population of CXCR4/CCR5-tropic HIV-1 isolates was detected in 5 subjects, including 3 subjects in the 40-

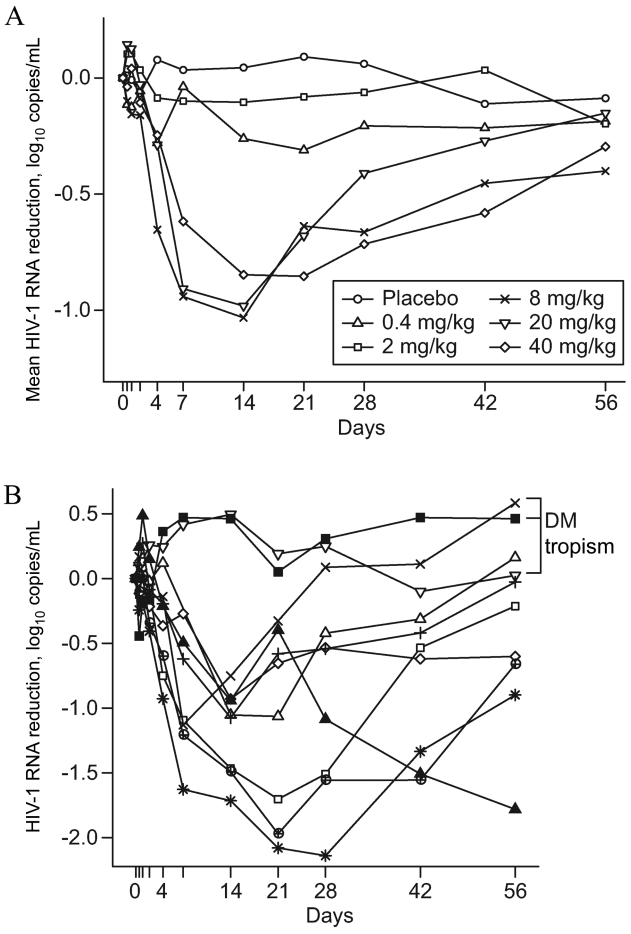

Figure 2. *A,* Mean HIV-1 RNA reduction observed during a 56-day period in patients receiving a single intravenous infusion of HGS004 (0.4, 2, 8, 20, or 40 mg/kg), compared with placebo. *B,* HIV-1 RNA reduction in individual subjects receiving the maximum single intravenous dose of 40 mg/kg. DM refers to the 3 subjects who had dual/mixed (CXCR4/CCR5)–tropic isolates detected during the study.

mg/kg group (figure 2*B*) and 1 subject each in the 20- and 0.4-mg/kg groups. Each of these subjects had a high baseline HIV-1 RNA level (4.5–5.1 $\log_{10}$ copies/mL), and in 1 subject a dual/mixed population was detected on day 0. None of the 5 subjects with a tropism shift had significant antiviral response. No tropism shifts were observed in subjects receiving placebo.

HGS004 serum levels and antiviral response. Because the maximum antiviral response was observed on day 14, a correlation analysis was performed to assess the association between HIV-1 RNA reduction on day 14 and HGS004 concentrations that exceeded the IC_{90} for each patient's clinical isolates. As shown in figure 3*A* a strong correlation was observed between reductions in HIV-1 RNA and drug concentrations relative to isolate sensitivity (C_{day14}/IC_{90}) in subjects who demonstrated a significant HIV-1 RNA reduction ($\geq$1 $\log_{10}$) on day 14 with HGS004 levels that were close to or exceeded the individual subject's clinical isolate IC_{90}(susceptibility to HGS004). The exposure-response relationship between antiviral activity on day 14 and HGS004 serum levels was explored using a maximum effect (E_{max}) model. As shown in figure 3*B*, the E_{max} model predicted that the maximum antiviral activity is estimated to be 1.31 $\log_{10}$ copies/mL. Given the correlation between antiviral response and serum drug levels, the susceptibility of individual subject HIV-1 isolates to a more potent fully human monoclonal antibody (HGS101) was assessed. As shown in figure 4, HGS101 demonstrated a median 5.5-fold greater in vitro activity. The potency was further enhanced (median, 7.3 fold) over HGS004 in isolates that were less susceptible to HGS004 (IC_{90} >50 μg/mL).

CD4 and CD8 cell counts. The changes in CD4 and CD8 cell numbers from baseline are shown in figure 5. Significant increases in both CD4 and CD8 cell counts were observed after the infusion of HGS004 in all dose cohorts. The overall mean maximal increase ranged from 155 to 224 cells/μL for CD4 cell

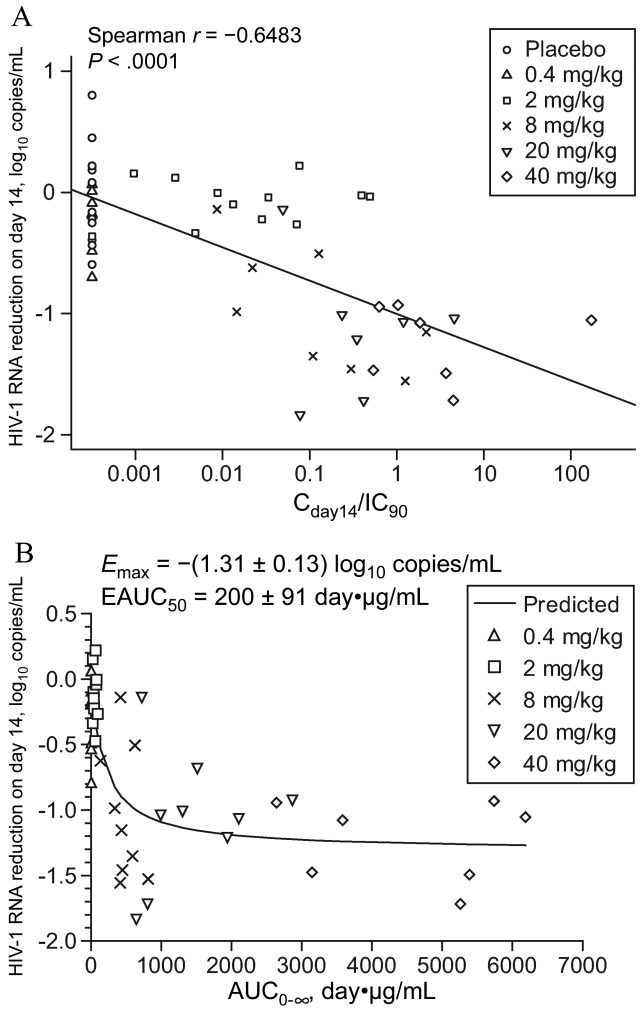

Figure 3. Pharmacodynamics of HGS004. *A,* Relationship of HIV-1 RNA reduction at day 14, serum HGS004 concentrations at day 14 (C_{day14}), and HIV-1 isolate susceptibility (IC_{90}) in individual subjects. *B,* Relationship of HIV-1 RNA reduction at day 14 and drug exposure (area under the curve [AUC]) in individual subjects. $EAUC_{50}$, AUC at 50% maximum effect; E_{max}, maximum effect.

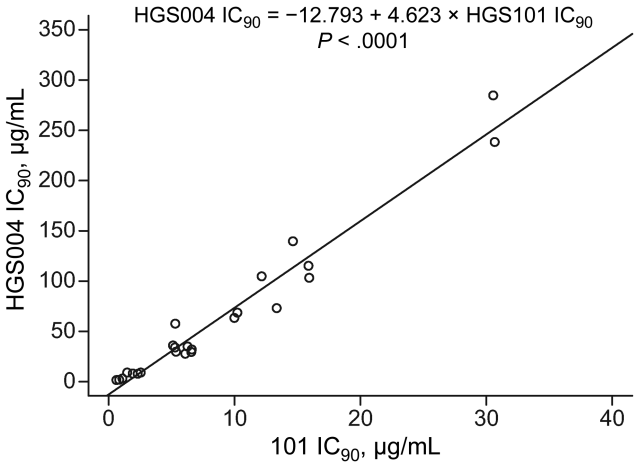

Figure 4. Comparison of the potency of monoclonal antibodies HGS004 and HGS101 on the basis of clinical isolate IC_{90} values in individual subjects.

counts and from 477 to 1045 cells/μL for CD8 cell counts across the 5 treatment groups. The increase from baseline values for both CD4 and CD8 cell counts persisted beyond day 28 for subjects in the high-dose cohorts (8, 20, and 40 mg/kg). In general, subjects who achieved an increase in CD4 cell count also showed an increase in CD8 cell count (data not shown). These significant changes in lymphocyte counts were not accompanied with any change in polymorphonuclear cell (e.g., neutrophil) counts. There was no clear correlation observed between the change in CD4 and CD8 cell counts and drug concentrations, receptor occupancy, or antiviral response.

DISCUSSION

The development of novel agents that inhibit HIV-1 replication by blocking its interaction with the CCR5 receptor has several potential advantages; these include a potentially higher genetic barrier against the development of viral resistance and synergy with other classes of antiretroviral agents, including other entry inhibitors. The recent demonstration of efficacy and safety with small-molecule allosteric inhibitors of CCR5, including the recent approval of maraviroc by the Food and Drug Administration [9–12], support the development of long-acting, competitive, direct inhibitors that provide additional advantages of lack of significant drug interactions, activity against resistant strains, and a route of administration that may improve compliance. Challenges that face the development of this class of agents include the restricted use in patients infected with CCR5-tropic virus, and potential concerns related to the selection of dual-tropic or X4-tropic virus. In this study, we have demonstrated that limited exposure to a wide dose range of HGS004, a fully human IgG4 CCR5 monoclonal antibody, is safe and well tolerated, although several questions were raised pertaining to the clinical pharmacology of the compound.

Pharmacokinetics and pharmacodynamic response. The nonlinear pharmacokinetic data of HGS004 observed across the 10-fold dose range are of interest. Dose-normalized AUC increased ~4-fold, and a similar decrease in clearance was observed between the 2- and 40-mg/kg doses. Similarly, high levels of receptor occupancy were achieved for ~6 days at 2 mg/kg, 26 days at 8 mg/kg, and 30 days at 20 and 40 mg/kg. Hence, multiple-dose exposure studies are indicated to explore further the apparently increasing saturation of the target receptor with higher HGS004 doses. Although there is a correlation between drug concentrations and antiviral activity (C_{day14}/IC_{90} ratio and E_{max} model), no clear dose response was observed between the 8-, 20-, or 40-mg/kg treatment groups. Moreover, only 55% of patients had a significant antiviral response ($\geq$1 $\log_{10}$ reduction in HIV-1 RNA level) with these doses. The lack of significant HIV-1 RNA reduction in some patients correlated well with individual isolate susceptibility (IC_{90}) to HGS004. Cumulatively, these finding indicate that the anti-HIV potency of HGS004 as a single agent may be suboptimal. The enhanced potency, espe-

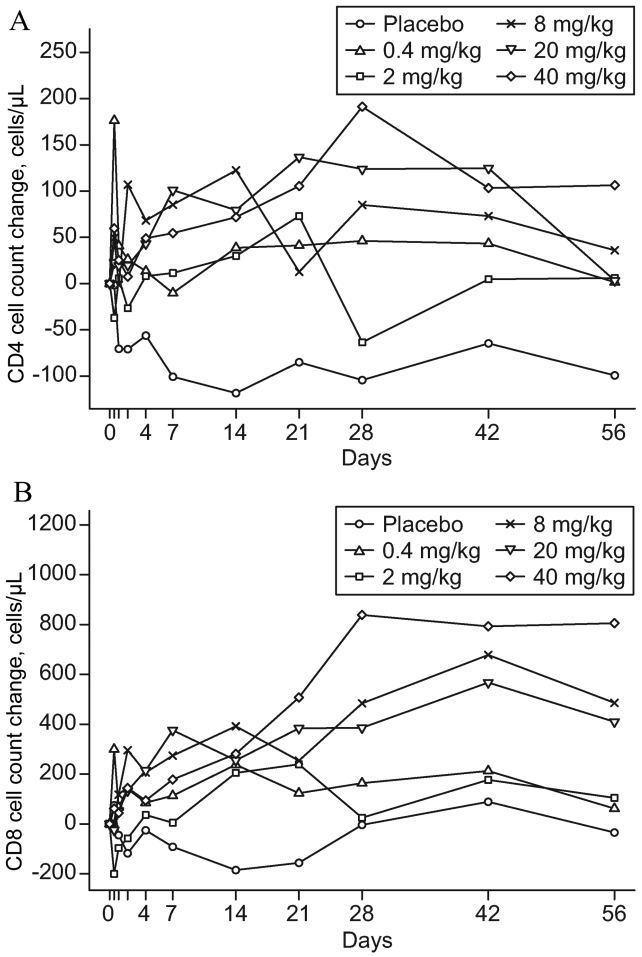

Figure 5. Mean change in CD4 *(A)* and CD8 *(B)* cell counts from pretreatment levels during a 56-day period in subjects receiving a single intravenous infusion of HGS004 (0.4, 2, 8, 20, or 40 mg/kg) or placebo.

cially in more resistant isolates of the second-generation monoclonal antibody HGS101, therefore makes this a promising candidate for future evaluation.

Shift in coreceptor tropism. A switch from CCR5 to CXCR4 tropism occurs spontaneously in ~50% of HIV-infected patients with advanced disease and has been associated with disease progression [16, 17]. A low frequency of detection of isolates demonstrating a tropism shift to a dual/mixed population was observed in this monotherapy study. We also did not observe a decrease in circulating CD4 T cell counts in persons in whom these shifts occurred. The majority of tropism shift occurred in the higher-dose cohorts, given the higher selection pressure with waning drug levels over a prolonged duration of up to 56 days. It should also be noted that when a CCR5 inhibitor is administered consistently as part of a combination treatment regimen, the emergence of X4-tropic viruses would not be selected for as readily [11, 12]. Nonetheless, further trials of these agents should be monitored carefully for the emergence of X4-tropic viruses and for the clinical implications of such occurrences.

CD4 and CD8 cell count changes. Another interesting observation in this study was the remarkable increase in circulating CD4 and CD8 cell counts in peripheral blood after administration of HGS004, even at the lowest dose. Increases were observed as early as day 1 and were maintained beyond day 28 in the higher-dose cohorts. It is likely that the increases are due to redistribution or altered trafficking of CCR5-expressing CD4 and CD8 cells from peripheral tissue to the vascular compartment. The long-term consequences of these observed changes on the immune status of patients will need further investigation. HGS004 is also a potent inhibitor of the binding of the 3 major CCR5 ligands (MIP-1α, MIP-1β, and RANTES) that bind to CCR5. These proinflammatory chemokines may contribute to the general state of immune activation that is thought to drive disease progression in HIV-1 infection [18–20]. This interesting activity of HGS004 must be explored further to define better the role of CCR5 antagonism in modulating the immune-activation state and its relationship to disease progression in HIV-1 infected patients.

In conclusion, this dose-ranging study provides proof of concept that HGS004, a fully human IgG4 monoclonal antibody against CCR5, is safe and demonstrates meaningful anti-HIV-1 activity. Further studies are warranted to explore further the antiviral activity of the more potent monoclonal antibody HGS101 and the possible immune-modulating properties of this agent in patients with HIV-1 infection.

Acknowledgments

We thank Drs. William Freimuth, Thi Migone, and Charles Hicks for useful discussions.

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