Pharmacokinetic and Pharmacodynamic Modeling of an Anti–Interleukin-6 Chimeric Monoclonal Antibody (Siltuximab) in Patients with Metastatic Renal Cell Carcinoma

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Abstract

Purpose: Interleukin-6 (IL-6) induces tumor growth, invasion, metastasis, and angiogenesis. Siltuximab (CNTO 328) is a chimeric, murine-human monoclonal antibody that specifically binds human IL-6 with high affinity. C-reactive protein (CRP) can be a pharmacodynamic (PD) marker of IL-6 bioactivity. Reductions in CRP may correlate with clinical activity and IL-6 bioactivity.

Experimental Design: Starting-dose selection for this study was based on a previous siltuximab study in multiple myeloma patients. Pharmacokinetic (PK)/PD modeling explored the relationship between siltuximab PK and CRP suppression following i.v. siltuximab infusion in a three-part phase I/II study in 68 metastatic renal cell carcinoma patients. Modeling results were then used to simulate and determine which siltuximab dosage regimens would maintain CRP suppression below the lower limit of quantification (4 mg/L). Siltuximab was given at 1, 3, 6, or 12 mg/kg at weeks 1 and 4 and then every 2 weeks for 2 cycles in part 1; at 3 or 6 mg/kg every 3 weeks for 4 cycles in part 2; and at 6 mg/kg every 2 weeks for 6 cycles in part 3.

Results: A two-compartment PK model adequately described the serum siltuximab concentration-time data. An inhibitory indirect response PD model examined the relationship between siltuximab concentrations and CRP suppression. PD parameter estimates seemed reliable and physiologically relevant. Simulations showed that 6 mg/kg siltuximab every 2 weeks or 9 mg/kg every 3 weeks would reduce serum CRP to below 4 mg/L.

Conclusions: Using a stepwise design, PK/PD modeling was used to select the dose levels in this study. Furthermore, PK/PD modeling results were used to help select doses to be used in future siltuximab clinical development.

Interleukin (IL)-6, a multifunctional cytokine with various systemic functions, is elevated in numerous infectious, inflammatory, and autoimmune diseases, and cancers. Considerable experimental and clinical evidence suggest a strong rationale for targeting IL-6 as a therapeutic strategy (1). In numerous preclinical models, binding IL-6 resulted in tumor regression or prolonged survival (2–5). There is evidence that IL-6 may be a critical mediator in the pathophysiology of renal cancer and that high levels of IL-6 correlate with metastatic progression and poorer prognosis (6). Elevated serum IL-6 is also associated with poorer response to IL-2 therapy (7).

IL-6 modulates the transcription of several liver-specific genes during acute inflammatory states (8). It has been shown that IL-6 is the primary inducer of C-reactive protein (CRP) synthesis by hepatocytes (9). Clinical investigations show that both serum IL-6 and CRP levels indicate disease severity and progression (10). In addition, elevated serum CRP levels were reported to correlate with serum IL-6 levels in various tumor types (8, 11).

Clinical investigations of monoclonal antibodies (mAb) against IL-6 in the treatment of cancers and related lymphoproliferative disorders have been conducted for more than one decade. Initial investigations conducted with murine mAbs to IL-6 (BE-4 and BE-8) in a single patient with primary plasma cell leukemia resistant to chemotherapy resulted in the inhibition of myeloma cell proliferation in bone marrow (12), showing the potential of anti–IL-6 mAb therapy. Subsequently, these mAbs were evaluated in multiple myeloma patients (13) and in HIV–1–positive patients with lymphoma (14), providing early evidence of preliminary clinical benefit in both indications. However, human antibodies to the BE-8 or the BE-4 mAb were detected in the HIV–1–positive patients. Moreover, BE-8 could not efficiently block daily production of IL-6 levels that are >18 μg/day (15). Lastly,
PK/PD Modeling of an Anti–IL-6 mAb in Metastatic RCC

Translational Relevance

The dose selection of most small-molecule agents used in the treatment of cancer is limited due to toxicity considerations, such that most agents are administered at the maximum tolerated dose. In contrast, the selection of dose level and dosing schedule for large molecule agents may not be limited by toxicity, and the selection of the optimal treatment regimen may require a thorough understanding of the pharmacokinetic (PK)/pharmacodynamic (PD) relationship. In this study, we described how PK, PD, and PK/PD modeling data can be applied in a prospective manner to assist in the selection of the dose and schedule of treatment regimens for an anti–interleukin-6 chimeric monoclonal antibody, siltuximab, in a complex three-part phase I/II study in patients with metastatic renal cell carcinoma. The developed PK/PD model can be extended to incorporate different tumor types or diseases with varying degrees of interleukin-6–related C-reactive protein production.

due to the short half-life of BE-8 (3-4 days), delayed IL-6 production may not be suppressed without repeated dosing (15), which is problematic because murine mAbs are generally neutralized by the human anti-mouse response ~2 weeks after starting treatment.

Siltuximab (previously called CNTO 328) is a chimeric mouse-human mAb to IL-6 that contains the variable antigen-binding region of the murine anti–IL-6 mAb and the constant region of the human immunoglobulin G1k (12). Siltuximab binds with high affinity and specificity to IL-6 (16). The first clinical study of siltuximab administered 2-hour i.v. infusions daily at 10, 20, or 40 mg in two 2-week cycles to 12 patients with multiple myeloma (17). This study showed the biological activity of siltuximab: a profound decrease in CRP levels was observed in all patients, but only minor effects on the M-protein were seen. This suggests that CRP can be used as a potential pharmacodynamic (PD) marker of IL-6 bioactivity. The median circulating half-life of siltuximab was 17.8 days. Siltuximab treatment was well tolerated and nonimmunogenic.

Although there was no evidence of an immune response noted in this study, it is likely that the high serum concentrations of siltuximab may have masked their detection. It is possible that long-term repeated dosing, which is common in cancer therapy, may eventually lead to the development of an immune response. The schedule of repeated daily dosing for 14 consecutive days at 4-week intervals used in these earlier trials is burdensome for both patients and clinicians. Therefore, in the current study, we explored alternative extended treatment schedules that would (a) allow for more convenient, less frequent dosing and (b) accommodate the dosing schedules of commonly used chemotherapeutic agents.

Based on evidence that IL-6 may be a critical mediator in the pathophysiology of renal cancer, because elevated IL-6 has been correlated with disease severity, and preclinical data showing siltuximab mediated inhibition of the growth of human renal carcinoma tumors in nude mice (4), a three-part, phase I/II study was conducted to evaluate the safety, efficacy, pharmacokinetics (PK), and PD of multiple i.v. infusions of siltuximab administered on a every-2-week or every-3-week schedule in patients with metastatic renal cell carcinoma (RCC; Rossi et al., in process). The starting dosage regimen for part 1 of this phase I/II study was selected in an attempt to sufficiently neutralize the circulating level and endogenous production of IL-6. During the previous study of siltuximab in patients with multiple myeloma, IL-6 levels reached 50 pg/mL, with median IL-6 production rates of 60 μg/day (16). In a clinical study of the murine anti–IL-6 mAb BE-8 in patients with metastatic RCC, total inhibition of CRP production was only achieved in patients producing <16 μg/day of IL-6 (13), which equates to a mean concentration of ~6 ng/mL per day, assuming a blood volume of ~3,000 mL. The 5-μg/mL siltuximab trough concentration initially proposed as a target for the starting dose of this study was based on maintaining at least a 300-fold molar excess of antibody to total serum concentration and IL-6 production. This excess quantity was considered necessary to block IL-6 activity to below the level required to support tumor growth (18) based on the dissociation constant of the anti–IL-6 antibody/IL-6 complex and the Law of Mass Action.

Maximum suppression of CRP concentrations to below the lower limit of quantification (LLOQ) throughout the dosing interval was anticipated to provide the best opportunity for siltuximab therapy to show clinical activity. Serum amyloid A (SAA), also induced by IL-6 as an acute phase inflammatory protein, and soluble IL-6 receptor (sIL-6R) were investigated as potential PD biomarkers of anti–IL-6 therapy because these biomarkers are likely more sensitive than CRP to IL-6 changes.

In this article, we report PK, PD, and PK/PD modeling results from a three-part phase I/II study in RCC patients. Our primary objective was to show how PK, PD, and PK/PD modeling data could be used in a stepwise manner to select treatment dosages in a clinical study. Our secondary objective was to apply the results generated from the PK/PD modeling to simulate clinically feasible dosage regimens that may be used in future siltuximab clinical development.

Materials and Methods

The phase I/II study of siltuximab in metastatic RCC

Study design. Details of the study design and the primary results are reported elsewhere (Rossi et al., in process). Key patient eligibility criteria included documented, progressive metastatic RCC and detectable CRP serum concentration (≥4 mg/L) according to a standard assay. Siltuximab was administered through 2-h i.v. infusion. In part 1, a phase 1, open-label dose-escalation design, siltuximab was administered at 1, 3, 6, or 12 mg/kg on days 1, 29,
43, and 57. The primary objective of part 1 was to obtain safety and single-dose PK. The enrollment of the 12-mg/kg cohort—which was to assess patients with high baseline serum CRP (≥50 mg/L)—in part 1 coincided with enrollment for part 2. In part 2, a phase II, double-blind, randomized design, siltuximab was administered to 37 patients at two of the higher dose levels selected from part 1: 3 or 6 mg/kg on days 1, 22, 43, and 64. In part 3, a phase II, open-label design, siltuximab was administered to an additional 20 patients at 6 mg/kg on days 1, 15, 29, 43, 57, and 71 to further examine the siltuximab activity at higher dose frequency (every 2 wk) in low-risk patients with serum CRP of ≤30 mg/L. In parts 1 and 2, patients' medical history and signs and symptoms were typical of a population with advanced stage RCC. However, at the time of enrollment for part 1, the Memorial Sloan-Kettering Cancer Center criteria were being developed and the criteria were not used to classify patients. In part 2, although the determination of this disease status was not directly related to the Motzer score (19), retrospective analysis estimated that one third of patients had a baseline Motzer score of 2. For part 3, patients were low risk with a baseline Motzer score of ≤1. The protocol for all parts of the study was approved by the Institutional Review Board at each site, and all patients provided written informed consent.

**Pharmacokinetics.** In part 1, serum samples were collected from all patients for PK analysis following the first and fourth siltuximab infusions; predose, 1, 2, 3, and 24 h postdose, and 2, 3, 7, 14, and 21 d postdose; immediately before and after all other infusions; and at the week 6 follow-up. In part 2, samples were collected before and 2, 3, 7, 14, and 21 d after the first infusion; immediately before and after the second and third infusions and each week after; and 1, 2, and 4 wk following the last infusion. In part 3, samples were collected before the first infusion and immediately, 6, and 12 h after; on days 3, 4, and 8; and immediately before and after the second, third, fourth, and fifth infusions. For the sixth infusion, samples were collected 1 h after the start of infusion; and immediately, 6, and 24 h, and 2, 3, 7, 14, 21, 28, and 42 d after. Siltuximab serum concentration was measured using a validated ELISA. The lower limit of detection for siltuximab was 0.05 μg/mL.

Noncompartmental analysis was conducted for parts 1 to 3 of the study using WinNonlin version 4.0.1 (Pharsight Corp.). The maximum observed concentration (Cmax) was obtained by evaluating each patient’s serum concentration-time profile. The area under the serum concentration-time curve from zero to infinity (AUC) and the area under the serum concentration versus time curve between two defined time points AUC(t1-t2) was calculated using the linear trapezoidal method. The terminal half-life (t1/2) was determined using linear regression of the time points judged by the terminal phase of disposition. The clearance (CL) and the volume of distribution (Vz) were calculated using standard noncompartmental methods.

**Pharmacodynamics.** Serum samples were collected from all patients ≤2 wk before the first infusion and during and between each administration visit. Following the first dose of siltuximab, all samples used for the measurement of CRP were obtained when siltuximab serum concentration samples were obtained. Serum concentrations of CRP and IL-6 were the primary PD markers. The LLOQ of the CRP method was 4 mg/L. SAA and other PD markers associated with IL-6 activity were also measured. CRP and SAA serum concentrations were analyzed.

![Graph](image-url)
using commercial ELISA kits (Quintiles Laboratories). Total serum IL-6 concentrations were determined using a high-sensitivity ELISA (R&D Systems). Free serum IL-6 concentrations, GP80, and sIL-6R were determined using ELISA kits.

**Modeling**

PK and PK/PD modeling was done with WinNonlin using available siltuximab and CRP serum concentration data from all patients following the first infusion. Several PK models were investigated during the model discrimination process, and the most appropriate one was chosen based on the law of parsimony (simplest model), the value of the Akaike information criterion test, and visual inspection of weighted residuals versus observed concentrations and fitted and observed siltuximab serum concentrations versus time. An i.v. infusion two-compartment model with first-order elimination was selected as the final PK model as follows:

\[
C = \left( \frac{Div}{Vc} \frac{K21}{\alpha - \beta} \right) \left( e^{-\alpha t} \right) + \left( \frac{Div}{Vc} \frac{\beta - K21}{\beta - \alpha} \right) \left( e^{-\beta t} \right)
\]

in which \( K10 \) is the rate constant of movement from compartment 1 to elimination, \( K12 \) is the intercompartmental rate from 1 to 2, and \( K21 \) is the intercompartmental rate from 2 to 1. In the above equation, \( C \) is the concentration, \( Div \) is the dose, \( Vc \) is the central compartment volume, \( \alpha \) is the initial slope (distribution), \( \beta \) is the terminal slope (elimination), and \( T \) is the time.

An inhibitory indirect response PD model was also developed using WinNonlin to characterize the relationship between siltuximab and the CRP serum concentration-time course. CRP serum concentrations below the LLOQ were treated as half that value, i.e., 2 mg/L. The equation of the inhibitory indirect response PD model is as follows:

\[
\frac{dR}{dt} = Kin \left( 1 - \frac{Cs}{IC50 + Cs} \right) - Kout \cdot R
\]

In the above equation, \( Kin \) is the zero-order constant for production of the response; \( Kout \) is the first-order rate constant for the loss of response; \( Cs \) is the siltuximab serum concentration; \( IC50 \) is the siltuximab concentration that produces 50% of maximum inhibition, achieved at the effect site; and \( R \) is the rate of response to CRP response. Based on the observed PK and PD parameter estimates, simulation was conducted to determine which clinically feasible dosage regimens would suppress CRP to below the LLOQ.

**Fig. 2.** Mean CRP serum concentration for patients in parts 1, 2, and 3. Arrows, administration of siltuximab infusion.
Statistical design

Descriptive statistics were used to summarize all data. No formal hypothesis testing was planned. Sample sizes were selected to obtain preliminary information regarding PK and PD data and were not based on statistical considerations.

Results

Baseline demographics for parts 1 to 3

Of the 11 patients treated in part 1, 9 were male. The median age was 60 years, and the median body weight was 77 kg. In part 2, 17 patients received 3 mg/kg and 20 patients received 6 mg/kg. Sixty-eight percent of these patients were male. The median age was 57 years, and the median weight was 82 kg at baseline. In part 3, all 20 patients received siltuximab at 6 mg/kg every 2 weeks. Nineteen patients were male. The median age was 62 years, and the median body weight was 86 kg. Based on correlation analysis, there seems to be a relationship between serum concentrations of CRP and IL-6 at baseline in parts 1 and 2 (Supplementary Fig. S1).

Part 1

Pharmacokinetics/pharmacodynamics. Based on a non-compartmental analysis, systemic exposure of siltuximab increased with dose (Fig. 1A) in terms of Cmax and AUC in an approximately dose-proportional manner (Supplementary Table S1); an exception was observed at the 12-mg/kg dose level, most likely because only three patients were available at this dose level. A steady state was not reached after four drug administrations. CL and Vz were considered to be independent of dose (data not shown). The mean t1/2 across all cohorts after the fourth dose was 17.35 days.

Mean CRP serum concentration was variable throughout the treatment period (Fig. 2A). PD evaluations indicated that serum CRP was not suppressed below the LLOQ by siltuximab at a dose of 1 mg/kg, whereas dosing at 3 or 6 mg/kg showed complete CRP suppression when a patient’s siltuximab serum concentration was ≥10 μg/mL at baseline, except in 1 patient who developed an infection during the study (data not shown).

Modeling. We used the mean PK data to simulate various clinically feasible doses and dosage regimens for which a target trough siltuximab serum concentration of 21 μg/mL was predicted to be effective in maintaining CRP below the LLOQ. Simulation data showed that siltuximab administration at 3 or 6 mg/kg every 3 weeks would achieve this target concentration (at trough) before the second infusion. This dose regimen was used for part 2.

Part 2

Pharmacokinetics/pharmacodynamics. PK results showed that systemic exposure (Fig. 1B) and derived parameters (Supplementary Table S1) increased with dose from 3 to 6 mg/kg. A steady state was not reached after four infusions. The terminal phase mean t1/2 ranged from 17.0 to 17.7 days. However, the washout period for the determination of the half-life was only 21 days, making it difficult to obtain an accurate t1/2 estimate. Treatment with siltuximab resulted in the sustained suppression of circulating CRP in both cohorts compared with baseline (Fig. 2B). However, adequate suppression was not shown in patients with baseline serum CRP of >30 mg/L in either cohort with this every-3-weeks dosage regimen (data not shown).
**Modeling.** The dose schedule for part 3 was planned to assess whether patients with baseline serum CRP of ≤30 mg/L had been given a sufficient amount of siltuximab to achieve treatment response. Based on PK modeling showing that 6 mg/kg siltuximab administered every 2 weeks would achieve a serum concentration of >21 µg/mL at all time points and PK/PD modeling showing that CRP would be suppressed to levels below the LLOQ after the first infusion and throughout the treatment period (Fig. 3), a more dose-intensive regimen of siltuximab at 6 mg/kg every 2 weeks was selected for part 3.

**Part 3**

PK evaluations (Supplementary Table S1; Fig. 1C) were similar to those from parts 1 and 2, with a steady state not being reached after six infusions were administered every 2 weeks. The mean t1/2 for this dose level was 13.5 days. However, the washout period for the determination of the half-life was only 14 days, making it very difficult to obtain an accurate estimate of the half-life. Administration of siltuximab at 6 mg/kg every 2 weeks seemed to effectively suppress serum CRP in all patients (Fig. 2C), all of whom had a baseline CRP of ≤30 mg/L according to the amended patient inclusion criterion for part 3.

**PK/PD Modeling for parts 1 to 3.** All patients with evaluable PK and PD data from parts 1, 2, and 3 were modeled on an individual basis using their paired PK and PD data. A representative individual PK/PD modeling example of siltuximab and CRP concentration-time profiles is shown, respectively, in Fig. 4A and B. The mean PK and PD parameters obtained from individual PK/PD modeling are presented in Table 1A and B, respectively. The mean
The dose selection of most small-molecule agents used in the treatment of cancer is limited due to toxicity considerations, such that most agents are administered at the maximum tolerated dose. In contrast, the selection of dose level and dosing schedule for large molecule agents may not be limited by toxicity, and the selection of the optimal treatment regimen may require a thorough understanding of the PK/PD relationship. In this study, we described how PK and PD data were used to select doses for each part of a phase I/II study of siltuximab in patients with metastatic RCC. In addition, PK/PD modeling was conducted to assist in the selection of the dosing regimen to be used in future clinical trials of siltuximab.

The starting dose of part 1 of this study was selected based on published data from van Zaanen et al. (17). Some associated risks were involved with using these data to predict the starting dose. The doses used in the study were not normalized to body weight, and the dose assumptions were based on the daily IL-6 production in patients with multiple myeloma, which differs from that of patients with RCC. However, the observed PK data from part 1 at the 1-mg/kg dose level agreed with the predictions, perhaps due to the relatively high degree of predictability of PK for large molecules.

As described earlier, clinical investigations have shown that serum IL-6 and CRP levels are correlated and are associated with disease severity and progression (10). Therefore, we monitored CRP as a PD marker of IL-6 bioactivity throughout this study. Although a definitive correlation between CRP response and clinical efficacy needs to be further established, several patients in this study who showed significant CRP response also showed stable disease, suggesting that monitoring CRP as a measure of IL-6 neutralization is a reasonable approach (Rossi et al., in process). SAA, another acute phase inflammatory protein that is induced by IL-6, was also inhibited by siltuximab treatment and may be yet another biomarker of IL-6 neutralization that warrants further exploration.

In an attempt to identify the optimal biomarkers of siltuximab treatment, we examined the concentrations of total IL-6, CRP, and SAA in this report. Changes in CRP and SAA were positively correlated (data not shown), and therefore, CRP can be used as a biomarker for siltuximab due to its accessibility and cost effectiveness in comparison.
Fig. 5. Mean percent change from baseline in SAA concentrations in parts 1, 2, and 3.
with SAA. In contrast, total IL-6 measurements, which always increased following siltuximab administration—reflecting drug and IL-6 immune complexes—did not provide an accurate assessment of circulating bioactive IL-6 levels or provide an estimate of the extent of IL-6 neutralization.

Serial PK samples were collected in all parts of this study to allow for a robust analysis of the PK of siltuximab. Dose-proportional increases in the Cmax and AUC (0-14d) were observed in this study. In patients with appropriate data, the terminal phase half-life encompassing all dose levels was ∼18 days and is in the range of that expected from endogenous IgG. For the 6-mg/kg dose level administered every 2 weeks, the degree of interpatient variability in terms of the percent coefficient of variance of the mean value for Cmax was 20.0% and AUC (0-14d) was 17.3%. This value is within the range of values that have been reported for antibodies targeting soluble targets in cancer patients. Due to the long half-life of siltuximab, a steady state was not achieved following repeated dosing. However, the increases in trough concentration were consistent with the terminal phase half-life, suggesting that time-dependent changes in PK did not occur. Siltuximab was well tolerated in all parts of this study, and a maximum tolerated dose was not established (Rossi et al., in process). In part 2, the primary efficacy criterion of tumor response including disease stabilization was met with one patient achieving a partial response for ∼8 months, and ∼50% of patients had stable disease that was sustained for a minimum of 11 weeks. Further information about the clinical response and toxicity data will be published separately.

Because all tested doses of siltuximab seemed to be safe (Rossi et al., in process), a good understanding of the PK/PD was needed to select the dose and dosing schedule for siltuximab administration. PK/PD modeling was conducted using individual data from all patients in this study. An indirect PK/PD model was chosen because a lag time between maximal siltuximab serum concentration and CRP inhibition was observed. The mean indirect response PK/PD model generated Kin (20 μg/L/d) and Kout (0.64 1/d) parameter values that were comparable with those reported in the literature (8 μg/L/d and 0.79 1/d, respectively; refs. 20, 21), suggesting that the model is of physiologic relevance. The maximal decrease in CRP would not be observed until 5 days after siltuximab dosing because the Kout parameter estimate corresponds to a half-life of ∼1 day. Because there were no time-dependent changes in the PK or the PD, using the single-dose PK/PD modeling data to simulate model dose seems to be valid.

Simulation based on the PK/PD modeling in RCC patients revealed that dosing of siltuximab at 6 mg/kg every 2 weeks or 9 mg/kg every 3 weeks would decrease CRP to below the LLOQ of 4 mg/L throughout the treatment period. Although CRP is not a validated biomarker in RCC patients, we believe that CRP suppression is a meaningful surrogate for showing the inhibition of IL-6 signaling. The PK/PD modeling supports using a dose that will inhibit IL-6 activity in RCC patients. These results are only readily applicable to RCC patients, and other tumor types or diseases with higher production of IL-6–related CRP may require higher doses of siltuximab. In addition, the CRP data used for the modeling were not from a high sensitivity assay, and if CRP data become available from a high sensitivity assay (i.e., LLOQ of 1 mg/L), we may need a higher dose of siltuximab to decrease CRP to below a more sensitive LLOQ.

We have summarized how PK, PD, and PK/PD modeling data can be applied in a prospective manner to assist in the selection of the dose and schedule of treatment regimens for siltuximab in a complex three-part phase I/II study in RCC patients. The developed PK/PD model can be extended to incorporate different tumor types or diseases with varying degrees of IL-6–related CRP production.

Disclosure of Potential Conflicts of Interest

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