ORIGINAL ARTICLE

Clinical pharmacokinetics of bevacizumab in patients with solid tumors

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Abstract

Objective To characterize the population pharmacokinetics of bevacizumab and the influence of demographic factors, disease severity, and concomitantly used chemotherapy agents on it's pharmacokinetic behavior.

Patients and methods Data from eight clinical trials with bevacizumab administered by intravenous infusion were included. A total of 4,629 bevacizumab concentrations from 491 patients with solid tumors, who received bevacizumab doses ranging from 1 to 20 mg/kg at a dosing frequency ranging from weekly to every 3 weeks, were analyzed using a nonlinear mixed-effects modeling approach (NONMEM).

Results The best structural model was a two-compartment model with first-order elimination. In the final model, estimated clearance (CL) and central compartment volume of distribution (V_c) were 0.207 L/day and 2.39 L for a typical female. The terminal half-life estimate was ∼20 days for both men and women. Body weight and gender were the most significant covariates to explain interpatient variability for CL and V_c. Clearance was 26% faster in men than in women. Patients with low serum albumin and high serum alkaline phosphatase had 19 and 23% faster CL, respectively, than a typical patient. Consistent with the long elimination half life, simulations showed that similar steady-state exposures can be maintained when the weekly mg/kg dose rate is maintained, therefore allowing administration of bevacizumab to coincide with the frequency of administration of the cytotoxic agents.

Conclusion The PK parameters were consistent with those of other IgG molecules. The results support dosing bevacizumab on a once every 2 weeks or once every 3 weeks dosing schedule on a mg/kg basis.

Keywords Population pharmacokinetics · Bevacizumab · Monoclonal antibody · Covariate effect · Dosing schedule

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Introduction

Bevacizumab (AVASTIN[TM], Genentech, Inc., South San Francisco, CA, USA), also known as rhuMAb VEGF, is a recombinant humanized IgG1 antibody that binds and inhibits effects induced by vascular endothelial growth factor (VEGF) in vitro and in vivo. Vascular endothelial growth factor, a diffusible glycoprotein produced by normal and neoplastic cells, is an important regulator of physiologic and pathologic angiogenesis [6]. A large, randomized, controlled Phase III clinical trial has demonstrated that the addition of bevacizumab (5 mg/kg every 2 weeks) to standard chemotherapy with the bolus-IFL [irinotecan/5-fluorouracil (5-FU)/leucovorin] regimen improves survival in patients with previously untreated metastatic colorectal cancer [10]. Bevacizumab is the first

Table 1 Summary of studies included in analysis

Study	Bevacizumab dose (mg/kg)	Dosing frequency	Concomitant chemotherapy	Sampling scheme frequency	Patients with PK data
Phase I					
AVF0737g: dose-escalation, solid tumors	1, 3, 10[a]	Once monthly, then weekly for 3 weeks	Single agent	Full profile[b]	25
AVF0761g: solid tumors	3	Weekly	Doxorubicin, carboplatin/ paclitaxel, 5-FU/LV	Full profile[b]	12
Phase II					
AVF0776g: dose-escalation, MBC	3, 10, 20	Every 2 weeks	Single agent	Multiple peaks and troughs	74
AVF0757g: combination, NSCLC	7.5, 15	Every 3 weeks	Carboplatin/paclitaxel	Multiple peaks and troughs	66
AVF0780g: combination, CRC	5, 10	Every 2 weeks	5-FU/LV	Multiple peaks and troughs	67
Phase III					
AVF2107g: combination, CRC	5	Every 2 weeks	5-FU/LV or 5-FU/LV/ CPT-11	Peaks and troughs at two cycles	236

5-FU 5-fluorouracil, *CRC* colorectal carcinoma, *HRPC* hormone refractory prostate carcinoma, *LV* leucovorin, *MBC* metastatic breast carcinoma, *NSCLC* non-small-cell lung carcinoma, *CPT-11* irinotecan

[a] Doses of 0.1 and 0.3 mg/kg that were also investigated in this study in 10 patients were not included in the analysis because bevacizumab clearance at these doses was faster and these doses were not evaluated in further studies

[b] Serial samples collected over 1 month after administration of either first or last dose. In the intensive sampling period in study AVF0737g samples for PK analysis were obtained during the first dose at time 0 (predose 1) and at 10 min; 1, 2, 5, and 8 h; and 1, 2, 4, 7, 10, 14, 21, and 28 days (predose 2) following the end of the infusion, while in study AVF0761g PK sampling for the dose administered on day 49 included predose and 10 min, 5 h, and 3, 7, 14, 21, and 30 days following the end of the infusion

biologic agent clinically proven to extend survival in metastatic colorectal cancer and is approved in the US as a first-line treatment for metastatic carcinoma of the colon or rectum in combination with intravenous 5-FU-based chemotherapy [2]. Recently, bevacizumab plus paclitaxel has also been demonstrated to provide a progression-free survival benefit over paclitaxel alone in first-line metastatic breast cancer [17] and to prolong survival in combination with chemotherapy (paclitaxel and carboplatin) relative to chemotherapy alone in patients with advanced nonsquamous non-small-cell lung cancer (NSCLC) [5].

The pharmacokinetic (PK) and pharmacodynamic (PD) information were collected during Phase I to Phase III trials in the development program. In a preliminary analysis of a dataset consisting of full profile data from 52 individual patients in Phase I and II trials, the PK of bevacizumab was best described by an open two-compartment model [9].

The primary objective of the present analysis was to utilize data pooled from eight clinical trials investigating several different bevacizumab dosing regimens, patient populations, and concomitant antineoplastic regimens to determine the population PK of bevacizumab and its relationship to demographics, pathophysiological covariates, disease severity, and combination therapy with various chemotherapy regimens.

Methods

Patient population and data collection

The concentration data analyzed were obtained from eight bevacizumab clinical studies: three trials in which the drug was used as a single agent and five in which the drug was administered concomitantly with five different cytotoxic chemotherapy regimens. All patients gave written informed consent and the study protocols were approved by the medical ethics committee in all study centers. A summary of studies included in the analysis is given in Table 1.

Phase I trials enrolled patients with various types of solid tumors [8, 14]. Phase II and Phase III trials were conducted in patients with colorectal carcinoma [10, 12], hormone refractory prostate carcinoma [16], metastatic breast carcinoma [15] and NSCLC [11]. In these studies, bevacizumab doses ranged from 0.1 to 20 mg/kg, and dosing frequency ranged from weekly to every 3 weeks. Bevacizumab was administered initially as a 90-min infusion. If this first infusion was well tolerated, the infusion duration could be decreased in 30-min decrements to a minimum duration of 30 min. Intensive PK samples were taken for the two Phase I trials and multiple peaks and troughs were obtained for Phase II and III trials. Data from

the ten patients, who received doses of 0.1 and 0.3 mg/kg were not included in this population PK analysis because bevacizumab clearance at both of these doses was approximately two to three times faster than at doses ≥1 mg/kg and these lower doses were not investigated further in any clinical trial.

Covariates and patient characteristics considered in the analyses are shown in Table 2. A total of 15 pathophysiologic covariates were tested on bevacizumab clearance and volume of distribution. The effect of chemotherapies on bevacizumab clearance was also assessed.

Assay method

For all studies, serum bevacizumab concentrations were determined at Genentech, Inc. using an enzyme-linked immunosorbent assay (ELISA) that used recombinant human VEGF (rhVEGF) for capture and a goat antibody to human IgG conjugated to horseradish peroxidase for detection [1]. The lower limit of sensitivity of this assay was 78 ng/mL. Concentrations of rhVEGF up to 500 ng/mL, which are 5–10,000 times higher than systemically circulating VEGF, have been shown to not interfere with the determination of bevacizumab concentrations. It is therefore unlikely that a patient's circulating VEGF would interfere with the determination of bevacizumab concentrations under these conditions.

Population PK analyses

The PK data were analyzed using the nonlinear mixed-effects modeling (NONMEM) program (Version V, level 1.0, GloboMax LLC, Hanover, MD, USA) [3] together with the S-PLUS (Insightful Corp., Seattle, WA, USA) programs for goodness-of-fit assessment and covariate model building. The first-order estimation method (FO) in NONMEM was used for model development. First-order conditional estimation method (FOCE) was used for the final model.

The following strategy was used to develop the final model. First, the structural PK model was developed (e.g., a one- or a two-compartment model). Significant pathophysiological covariates were then identified and incorporated into the model, followed by assessment of the influence of combination chemotherapy on bevacizumab disposition to yield the final model. The final model was then evaluated with bootstrap for its robustness.

Interpatient variability in the PK parameters was assumed log-normally distributed (exponential model). For example, CL:

Table 2 Patient characteristics

Characteristic	Value
Gender	
Male	215
Female	276
Race	
Caucasian	416
Black	47
Hispanic	17
Asian	0
Native American	0
Other	11
ECOG performance status	
0	265
1	217
2	9
Chemotherapy (CHEM)	
0 = saline (single-agent)	104
1 = 5-FU/LV	152
2 = carboplatin/paclitaxel	64
3 = capecitabine	35
4 = doxorubicin	4
5 = bolus-IFL	132
Weight (WT, kg)	74 (49–114)
Height (HT, cm)	168 (155–188)
Body surface area (BSA, m^2)	1.84 (1.48–2.34)
Lean body mass (LBM, kg)	54 (39–74)
Serum-asparate aminotrasferase (SGPT, U/L)	26 (15–115)
Serum-alanine aminotransferase (SGOT, U/L)	23 (10–81)
Serum-alkaline phosphatase (ALK, U/L)	102 (59–483)
Serum Serum-bilirubin (mg/L)	4.0 (2–11)
Total protein (g/L)	72 (62–83)
Albumin (ALBU, g/L)	37 (29–44)
Creatinine clearance (CRCL, mL/min)	99 (54–175)

$N = 491$; values for categorical variables are numbers of patients; values for continuous variables are medians with 95% CI

$$CL_j = \hat{CL}_j \exp(\eta_{j,CL})$$

where $\eta_{j,CL}$ denotes the proportional difference between the "true" parameter (CL_j) of individual patient j and the typical value $\hat{CL}_j$ in the population, adjusted for values of covariates equal to those of the individual patient. The ηs represented random effects with mean zero and variance ϖ^2.

Residual error was modeled as a combination of proportional and additive components.

$$Cp_{ij} = \hat{Cp}_{ij}(1 + \varepsilon_{ij,prop}) + \varepsilon_{ij,add}$$

where Cp_{ij} and $\hat{Cp}_{ij}$ are the ith measured and model predicted (true) concentrations, respectively, for patient j, and

$\varepsilon_{ij,\mathrm{prop}}$ and $\varepsilon_{ij,\mathrm{add}}$ denote the proportional and additive residual intraindividual random errors, distributed with zero means and variances δ^2_{prop} and δ^2_{add}.

Covariate model development

The covariate effect analysis was limited to CL and V_c. Following identification of the basic structural model, individual patient random effects and PK parameter estimates were generated using post hoc Bayesian estimation. Graphs of random effects (e.g., $\eta_{j,\mathrm{CL}}$) versus covariates were produced with a smoothing of the data (SUPSMU function in S-plus) to allow visual inspection of the influence of covariates on the PK parameters.

The construction of the regression model for CL and V_c of bevacizumab using NONMEM was based on the likelihood ratio test. The objective function value (OFV) is

$$\hat{\mathrm{CL}}_j = \theta_1 \left(\frac{\mathrm{WT}_j}{\mathrm{med(WT)}} \right)^{\theta_{\mathrm{WT}}} \left(1 + \theta_{\mathrm{GDR}} \mathrm{GDR}_j \right)$$

where θs are the regression coefficients to be estimated for continuous (e.g., WT) or dichotomous (e.g., GDR) covariates. Continuous covariates were centered around their median [med(WT)] values, thus allowing θ_1 to represent the clearance estimate for the typical patient with median covariates. Dichotomous covariates were coded 0 or 1 (e.g., 0 = female; 1 = male).

The effect of chemotherapy on CL was tested last. Five different combination chemotherapy regimens were used in different trials (see Table 1). The regimen used in the pivotal study (i.e., the bolus-IFL regimen) was used as the reference and was compared with either bevacizumab as a single agent or bevacizumab when combined with all other chemotherapy regimens. The chemotherapy effect was implemented as shown below:

$$\mathrm{CHEMEF} = \begin{cases} 1, & \text{if bevacizumab } + \text{ IFL (reference)} \\ 1 + \theta_{14}, & \text{if bevacizumab only} \\ 1 + \theta_{15}, & \text{if bevacizumab } + \text{ all other chemotherapy than IFL} \end{cases}$$

proportional to the -2 times the log-likelihood of the data, given the model; therefore, the difference between two hierarchical models in OFV (ΔOFV) is approximately χ^2-distributed. When comparing two models, where the more complex model included one more parameter than the simpler one, the more complex model was selected only when the ΔOFV was greater than 7.88 ($df = 1$, $P < 0.005$). Use of this rather strict criterion was motivated by the multiple testing involved in the model development, as well as the fact that the ΔOFV is only approximately χ^2-distributed [7, 20].

The regression model for CL and V_c was constructed in three steps: (a) screening of covariate effects on CL and V_c separately, by adding covariates one by one to the base model; (b) construction of the full model by incorporating the significant covariates from step (a); (c) elaboration of the reduced model, by testing the full model against restricted models by removing each covariate one at a time. The reduced models obtained separately for CL and V_c at (c) were then combined in a new full model, and the final model for pathophysiological covariates was elaborated by testing the full model against restricted models by removing each covariate one at a time.

A multiplicative covariate regression model was implemented as follows [e.g., weight (WT) and gender (GDR) effect on CL]:

Simulation of temporal dosing patterns

Based on the final model, a total of 500 patients were randomly drawn from the pivotal Phase III study with replacement. The steady-state PK profiles in 500 patients following administration of 2.5 mg/kg per week (i.e., 5 mg/kg every 2 weeks and 7.5 mg/kg every 3 weeks) were simulated with parameters drawn from the population distribution of the final model. The difference in steady-state exposure for the two dosing regimens was evaluated and compared with the observed concentrations.

Results

Population PK analysis

The final dataset for analysis contained 4,629 concentrations from 491 patients, with treatment dose ranging from 1 to 20 mg/kg. On average, approximately 9.4 samples were available per patient (range 1–36), with collection time up to 1 year (97.5 percentile of 382 days). The important demographic and other baseline characteristics are summarized in Table 2. The patient population was predominantly Caucasian (85%) and female (56%), with a

median age of 59 years and median weight of 74 kg. There were several types of carcinomas; the majority of patients (79%) received bevacizumab in combination with various chemotherapy regimens.

A two-compartment model was found to describe the data better than a one-compartment model, with a decrease in objective function (OFV) of 1,173, and therefore was used as the base model. Sixteen pathophysiological covariates were evaluated for bevacizumab CL and V_c. Body weight (WT), gender, and albumin had the largest effect on CL. In addition, alkaline phosphatase and SGOT had significant effects on CL, and body weight, gender, and albumin had significant effects on V_c.

The effect of chemotherapy on CL was tested last, and was significant (ΔOFV > 62.7, df = 2, P < .005). However, as indicated by overlap in the parameter estimates, single-agent CL was not different from CL with the reference bolus-IFL regimen, while the CL with the bolus-IFL regimen was slower than that with all other chemotherapy regimens. Combined chemotherapy effect (CHEMEF) was incorporated to obtain the final model for CL and V as follows:

$$\hat{CL} = \theta_1[1 + (\theta_5 GDR)](WT/74)\theta_6(ALBU/37)\theta_7$$
$$(ALK/102)\theta_9(SGOT/26)\theta_{10}(CHEMEF)$$
$$\hat{V}_c = \theta_2[1 + (\theta_{11}GDR)](WT/74)\theta_{12}(ALBU/37)\theta_{13}$$

where GDR is gender, WT is body weight, ALBU is albumin, ALK is alkaline phosphatase, SGOT is serum glutamic oxalacetic transaminase, and CHEMEF is the effect of concomitantly administered chemotherapies on bevacizumab.

The final model using FOCE provided very similar parameter estimates when compared with FO. Parameter estimates from the final model and the 95% confidence interval from the bootstrap are shown in Table 3. The covariate effects in the final model explained about 40% of interpatient variance for V_c and 60% of interpatient variance for CL. Body weight and gender were the most significant covariates to explain interpatient variability for both CL and V_c. Bevacizumab CL was 26% faster in males relative to females. In the final model, estimated CL and V were 0.207 L/day and 2.39 L for a typical female, and 0.262 L/day and 3.29L for a typical male. The median terminal half-life estimate, based on the final model individual predicted values, was 19.9 days and similar for both genders (males 19.5 days, females 20.6 days).

Subjects with low serum albumin (a value <29 g/L) had a 19% faster CL, while patients with higher ALK (>483 IU/L) had a 23% faster CL than a typical patient.

Although there was significant effect of chemotherapy, single-agent CL was not different from the reference

Table 3 Population PK parameters from final model and 95% CI from the bootstrapping of final model

Parameter		Final model point estimates (95% CI from bootstrap)
Typical CL (L/day)	θ_1	0.207 (0.188, 0.226)
GDR on CL	θ_5	0.264 (0.132, 0.398)
WT on CL	θ_6	0.368 (0.088, 0.650)
ALBU on CL	θ_7	0.726 (0.472, 1.02)
ALK on CL	θ_9	0.133 (0.070, 0.206)
SGOT on CL	θ_{10}	0.0715 (0.002, 0.144)
CHEM on CL (1, 2, 3, 4 vs. 5)*	θ_{15}	0.174 (0.096, 0.244)
Typical V_c (L)	θ_2	2.66 (2.57, 2.76)
GDR on V_c	θ_{11}	0.221 (0.173, 0.285)
WT on V_c	θ_{12}	0.411 (0.284, 0.490)
ALBU on V_c	θ_{13}	−0.333 (−0.461, −0.242)
K_{12} (day^{-1})		0.223 (0.134, 0.501)
K_{21} (day^{-1})		0.215 (0.138, 0.416)
ω_{CL} (%)		26.0 (22.6, 30.7)
ωV_c (%)		16.8 (14.4, 19.8)
σ_{prop} (%)		17.2 (15.8, 19.0)
σ_{add} (µg/mL)		7.2 (0.093, 10.3)
K_{10} (day^{-1})		0.0779 (0.0696, 0.0861)
$t_{1/2\alpha}$ (days)		1.44 (0.72, 2.22)
$t_{1/2\beta}$ (days)		19.9 (17.9, 22.5)

*There is no difference in CL between patients treated with single-agent bevacizumab and in combination with IFL (CHEM = 0 vs. 5)

bolus-IFL regimen (95% CI of parameter estimate includes 0), while the CL in the bolus IFL regimen was 17% slower compared to all other chemotherapy regimens combined.

Evaluation of the final model

Figure 1 shows the goodness-of-fit for the final model. The IWRES versus IPRED plots suggested no significant deviations of IWRES from the line of identity, with the exception of a slight overproduction at low concentrations (also seen in the plot of IPRED vs. DV). However, no such trend was observed in the plot of WRES versus PRED, suggesting that the model can adequately predict low and high concentrations. The IWRES is calculated based on the following equation:

$$IRES = IPRED - DV, \quad W = IPRED, \quad IWRES = IWRES/W$$

Simulation results

While the steady-state peak concentrations were approximately 20% higher with dosing of 7.5 mg/kg every 3 weeks compared with dosing of 5 mg/kg every 2 weeks

Fig. 1 Model diagnostic plots. **a** Observed versus predicted bevacizumab concentrations. The *solid line* is the line of unity. **b** Weighted residuals versus predicted bevacizumab concentrations. The *dashed line* is a LOESS smooth of data
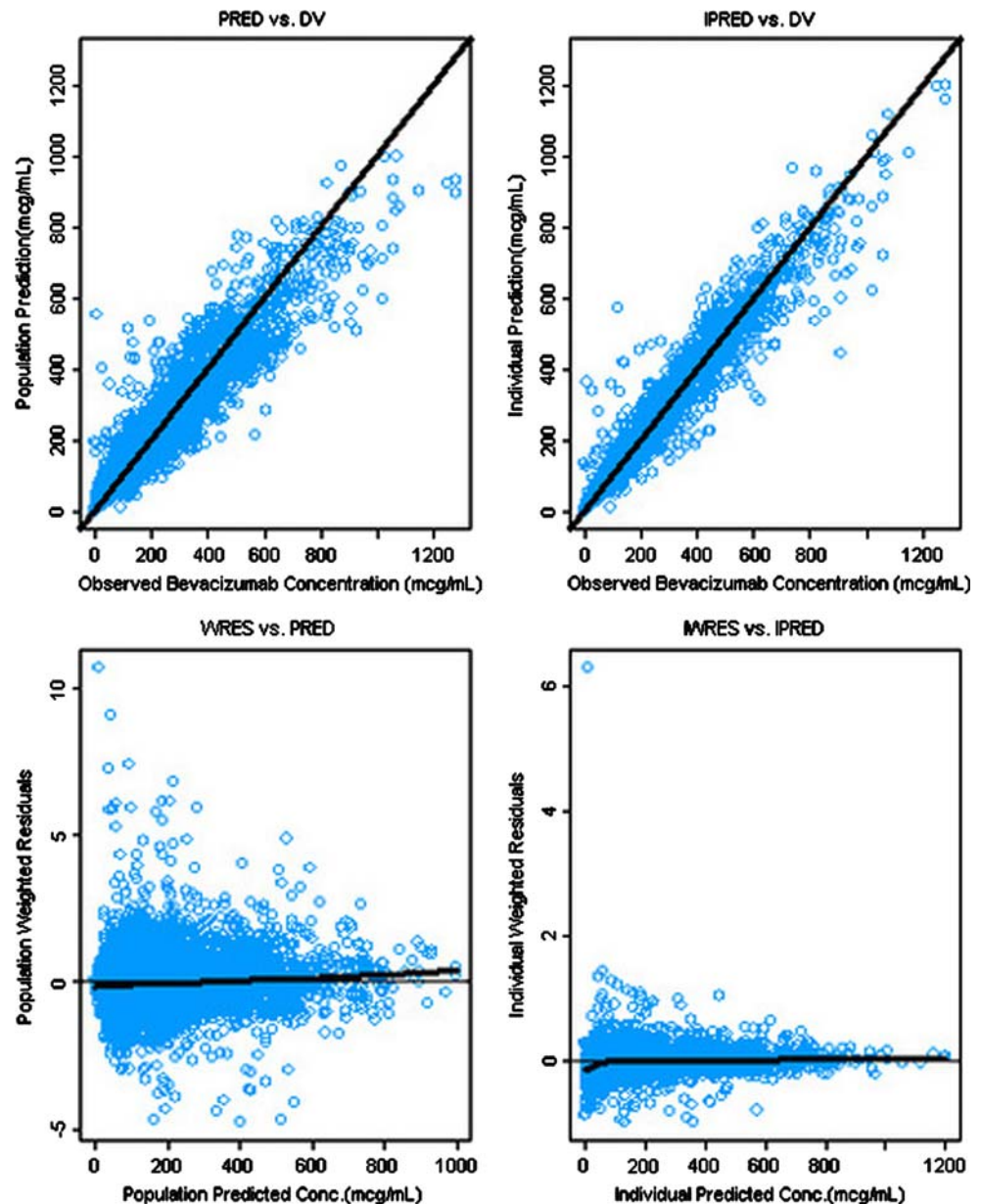
(270 vs. 215 µg/mL), the steady-state average and trough concentrations were similar for the two regimens (73 vs. 85 µg/mL).

Discussion

The population PK analysis combined data representing both single- and multiple-dose administration and rich and sparse data, and took advantage of drug accumulation information to estimate the long half-life of bevacizumab. In addition, the effect of pathophysiological covariates and concomitant therapy on PK parameters in the target patient population was evaluated.

Among all covariates tested, body weight and gender were the most important for explaining interindividual variability for CL. The CL of bevacizumab for extreme body weight (from 49 to 114 kg) was up to 30% around the typical value. After adjusting for weight, gender remained a significant effect, with a 26% faster CL in males than in females. The gender difference in bevacizumab clearance may be related to greater muscular mass in males than in females.

Patients with low serum albumin concentrations ($\leq$29 g/L) or a high concentration of serum alkaline phosphatase ($\geq$483 U/L) had approximately a 20% increase in CL compared with a typical patient. Low albumin (a sign of inflammation) and high alkaline phosphatase might be

Fig. 2 Comparison of model predicted steady-state concentrations following 5 mg/kg every 2 weeks (*left*) and 7.5 mg/kg every 3 weeks (*right*) dosing of bevacizumab
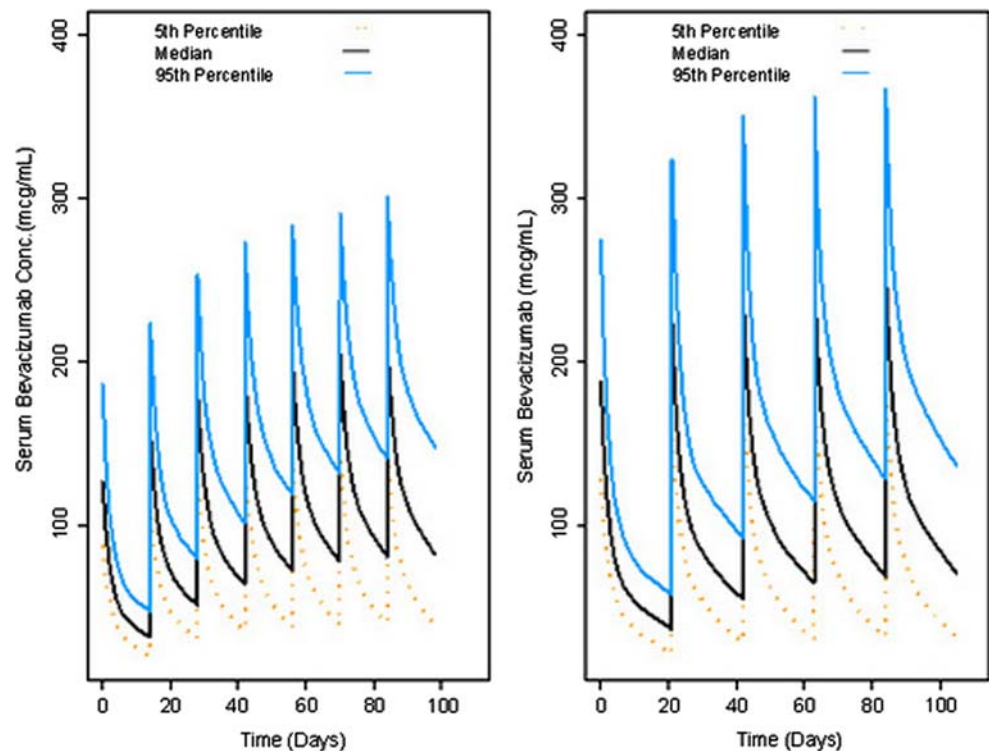
related to disease severity, and were correlated with tumor burden in this dataset. Tumor burden could not be assessed as a covariate for CL in this analysis since data were not available in all studies. Another measure of patients' disease severity, ECOG performance status, was tested and was not significant. It should be noted that only nine patients had an ECOG status >2, which may explain the apparent lack of relationship for this measure of disease severity. The effect of SGOT was of limited magnitude, with a 10% decrease in CL in patients with elevated SGOT (114 U/L). It is presently unknown if impaired liver function significantly alters the CL of bevacizumab, but is not considered likely, as bevacizumab complexes are cleared by the Fc receptor within the endothelial system and not the hepatocyte or biliary system per se [18]. Our preclinical data indicated that hepatic dysfunction resulting from bile duct ligation did not have a significant effect on bevacizumab PK in a rodent model [13]. Although different combination therapies were given to patients with different tumor types, the effect of chemotherapy on bevacizumab CL was minimal. Clearance of bevacizumab following repeated administration of the bevacizumab/bolus-IFL regimen combination in colorectal cancer patients was similar to that following treatment with bevacizumab as a single agent.

Despite these covariate effects, however, from a PD point of view these effects would have minimal effect on the level of unbound VEGF. Although concentrations of unbound (i.e., free) circulating VEGF could not be measured in clinical trials after bevacizumab treatment, based on the proposed clinical dose rates of 2.5 mg/kg per week in colorectal cancer and 5 mg/kg per week in breast cancer and NCSLC and the apparent IC50 of bevacizumab for VEGF, the circulating VEGF is predicted to be, on average, >98% bound with bevacizumab [1]. These data suggest that a 20–30% potential change in CL would not have a significant impact on the free fraction of VEGF and therefore the impact of these covariates on efficacy would be minimal. The definition of population PK model and covariates impacting bevacizumab disposition provides an important tool for the simulation of alternative dose schedules for future study.

In summary, the accumulation of bevacizumab to steady state concentration after long-term treatment can be predicted by a linear two-compartment model. The population PK parameters for bevacizumab are similar to those for other IgG antibodies [4, 19]. Weight and gender were the covariates with the greatest influence on bevacizumab CL and V_c, which support body weight based dosing of bevacizumab. Since bevacizumab display linear PK, similar exposure can be achieved with flexible dosage regimens administered on a mg/kg basis, such as Q2, or Q3 weekly dosing (Fig. 2).

investigators, the clinical research support teams, and to the patients participating in these trials.

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