Published OnlineFirst April 3, 2013; DOI: 10.1158/1078-0432.CCR-12-3829

Cancer Therapy: Clinical

Clinical Cancer Research

Evaluation of Food Effect on Pharmacokinetics of Vismodegib in Advanced Solid Tumor Patients

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Abstract

Purpose: Vismodegib, an orally bioavailable small-molecule Smoothened inhibitor, is approved for treatment of advanced basal cell carcinoma (BCC). We conducted a pharmacokinetic study of vismodegib in patients with advanced solid tumors to explore the effects of food on drug exposure.

Experimental Design: In part I, patients were randomized to fasting overnight (FO), a high fat meal (HF), or a low fat meal (LF) before a single dose of vismodegib 150 mg. Plasma concentrations of vismodegib were determined by a validated liquid chromatography-tandem mass spectrometry assay. Primary endpoints were C_{max} and area under the curve (AUC_{0-168}). In part II, patients randomized to FO or HF in part I took vismodegib 150 mg daily after fasting; those randomized to LF took it after a meal. Primary endpoints after two weeks were C_{max} and AUC_{0-24}.

Results: Sixty (22 FO, 20 HF, 18 LF) and 52 (25 fasting, 27 fed) patients were evaluable for primary endpoints in parts I and II, respectively. Mean C_{max} and AUC_{0-168} after a single dose were higher in HF than FO patients [ratios of geometric means (90% CI) = 1.75 (1.30, 2.34) and 1.74 (1.25, 2.42), respectively]. There were no significant differences in C_{max} or AUC_{0-24} between fasting and fed groups after daily dosing. The frequencies of drug-related toxicities were similar in both groups.

Conclusions: A HF meal increases plasma exposure to a single dose of vismodegib, but there are no pharmacokinetic or safety differences between fasting and fed groups at steady-state. Vismodegib may be taken with or without food for daily dosing. *Clin Cancer Res; 19(11); 1–9. ©2013 AACR.*

Introduction

The increasing use of oral anticancer drugs has made it important to discern whether or not concomitant food intake has a significant effect on the pharmacokinetics and safety profile of these drugs. Although this has been the case with oral drugs in other fields for many years, food effects have generally not been considered in the labeling of anticancer drugs (1). Drugs with low water solubility and high cell membrane permeability, such as tyrosine kinase inhibitors, are particularly susceptible to food effects, especially when a high fat meal (HF) is consumed. In recent years, it has been documented that a number of kinase inhibitors approved by the U.S. Food and Drug Administration (FDA) are subject to significant food effects on plasma exposure. The most striking example is lapatinib, which has a 150% increase in exposure (area under the curve; AUC) with food (2). Other kinase inhibitors with significant food effects include erlotinib, pazopanib, and nilotinib (3–5).

Food may affect pharmacokinetics by any or all of the following mechanisms: delaying gastric emptying, stimulating bile flow, changing the pH of the gastrointestinal tract, increasing splanchnic blood flow, changing luminal metabolism of a drug, and physically/chemically interacting with a dosage form or drug (6). FDA recommends that studies report the ratio of geometric means between groups for exposure parameters such as C_{max} and AUC, together with 90% confidence intervals, with a ratio of 80% to 125% establishing bioequivalence and ratios outside of that range establishing a significant food effect (FDA Guidance for Industry entitled "Food Effect Bioavailability and Fed Bioequivalence Studies," 2002).

There are multiple reasons for wanting to better understand the effects of food on drug exposure. First, there may be safety risks from increased exposure due to lack of adherence with a requirement for fasting. For example, as

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Prior presentation: Presented, in part, at the 48th Annual Meeting of the American Society of Clinical Oncology, 2012 Jun 1–5, Chicago, IL.

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Translational Relevance

Vismodegib was recently approved by the U.S. Food and Drug Administration for the treatment of advanced basal cell carcinoma, and is being studied in clinical trials for other solid tumors. Before its approval, we initiated a pharmacokinetic study in patients with advanced solid tumor to determine whether there is a significant effect of food on drug exposure, an issue of growing awareness and importance for all oral anticancer drugs. We found that a high fat meal increases exposure after a single dose of vismodegib compared with fasting, but there are no significant differences in drug exposure between fasting and fed groups after daily dosing. These data were the basis of the statement in the prescribing information that vismodegib may be taken with or without food.

nilotinib has a known risk of QT interval prolongation, the FDA has required the drug sponsor to institute a Risk Evaluation and Mitigation Strategy to assess and mitigate the potential risk of sudden death due to concomitant food intake (7). Second, there may be a financial incentive for payors to conduct food effect studies. For example, abiraterone acetate is labeled to be taken fasting despite the presence of a large (5 to 10-fold, depending on fat content of the meal) food effect. An ongoing, noninferiority study (NCT01543776) is randomizing patients to the labeled dose (1,000 mg fasting) versus a lower dose (250 mg with food). If the lower dose is noninferior with respect to the early change in prostate-specific antigen endpoint, a follow-up study could be done to establish whether the lower dose with food could be used routinely with significant potential cost savings for payors and patients (8).

Vismodegib is an orally bioavailable small-molecule Smoothened inhibitor that is thought to target cancer stem cells through the Hedgehog signaling pathway. At an oral dose of 150 mg daily, the drug has an acceptable safety profile and considerable activity in locally advanced (response rate of 43%) and metastatic (response rate of 30%) basal cell carcinoma (BCC; ref. 9). On January 30, 2012, the drug was approved by FDA "for the treatment of adults with metastatic BCC, or with locally advanced BCC that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation" (vismodegib prescribing information).

The pharmacokinetics of vismodegib are characterized by less than dose-proportional increases in plasma concentration with increasing dose and lower than expected accumulation after continuous daily dosing, suggesting nonlinear pharmacokinetics. The nonlinear pharmacokinetics of vismodegib result from 2 separate, nonlinear processes: (i) saturable absorption and (ii) high-affinity, saturable protein binding. Nonlinear absorption is consistent with the poor solubility of vismodegib at physiologic pH and likely resulted in a lack of dose-proportional increase in exposure after single doses of 270 mg and 540 mg. After multiple doses, vismodegib exhibits saturable binding to alpha-1-acid glycoprotein (AAG), which results in concentration-dependent changes in the pharmacokinetics of vismodegib. Under steady-state conditions with daily dosing, the concentration of unbound drug is a constant proportion of total drug concentration (10, 11). As the drug is a Biopharmaceutics Classification System class 2 compound (high permeability, low solubility) and has solubility-limited absorption, it is at risk for having a significant food effect. We designed and conducted a pharmacokinetic study to test the hypothesis that there is a significant food effect with single and/or daily dosing of vismodegib. The results of this study were the basis for the instructions regarding food in the prescribing information for vismodegib.

Materials and Methods

Study design

The primary objectives of this study were to evaluate the effects of prandial state and fat content of meals on the pharmacokinetic parameters of vismodegib. The secondary objectives were to evaluate the effects of prandial state on the safety profile of vismodegib, as well as to describe the anticancer activity of vismodegib in patients with advanced solid tumors. Key inclusion criteria were as follows: histologically confirmed advanced cancer (except for leukemias) refractory to standard of care therapy, or for which no standard of care therapy is available; measurable or nonmeasurable disease; Karnofsky performance status >70%; and normal organ and marrow function (leukocytes $\geq$3,000/μL; absolute neutrophil count $\geq$1,500/μL; platelets $\geq$100,000/μL; total bilirubin within normal institutional limits AST/ALT $\leq$2.5 times institutional upper limit of normal; creatinine $\leq$1.5 times institutional upper limit of normal). Because of the potential for drug–drug interactions, patients with medical conditions requiring treatment with a strong inhibitor or inducer of CYP3A4 or CYP2C9 were excluded.

The original study design was as follows. In part I, which lasted for 7 days, patients were randomized 1:1 to fasting overnight (FO) or a HF before a single dose of vismodegib 150 mg. In both groups, vismodegib was taken with 240 mL (8 fluid ounces) of water and no food was allowed for at least 4 hours post dose. Patients in the FO group took vismodegib after FO for at least 10 hours. Patients in the HF group took vismodegib 30 minutes after a meal consisting of 2 eggs, 2 strips of bacon, toast with butter, 113 g hash brown potatoes, and 228 g whole milk; this meal provides approximately 800 to 1,000 calories with approximately 50% of the calories from fat. In part II, which lasted for 28 days, patients randomized to FO in part I took vismodegib 150 mg daily after fasting (as above); those randomized to HF took vismodegib 30 minutes after a recommended meal (a guideline with several examples of a "healthy breakfast" was given to patients). Patients were asked to record the time and date of all vismodegib doses in a medication diary and the time, date, and content of all meals in a food diary and submit both diaries at each visit.

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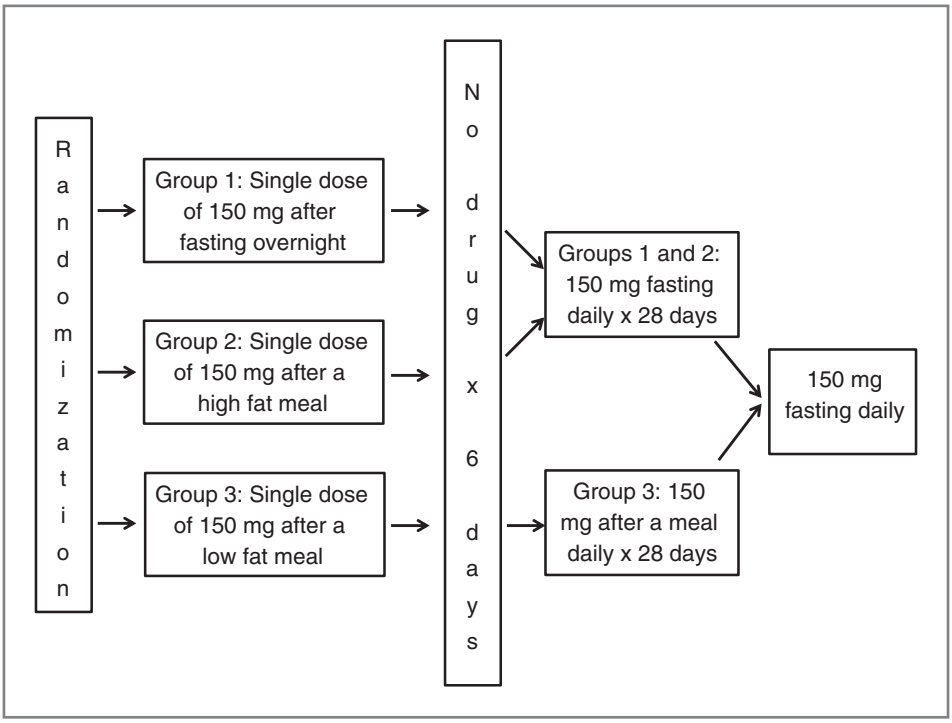

Figure 1. Study schema (postamendment).

The study was amended after enrollment of 24 patients to additionally test the hypothesis that a low fat meal (LF) before a single dose would have a significant food effect compared with FO. Calorie and fat content of meals may have significant implications for the bioavailability of a drug, as different types of meals are likely to have varying impacts on gastrointestinal physiology in relation to a drug disposition (6). If there is a food effect with vismodegib, it is important to know if the magnitude of effect (compared to fasting) is similar for LFs and HFs. After the amendment, the study design was as depicted in Fig. 1. In part I, which lasted for 7 days, patients were randomized 1:1:2 to FO, HF, or LF before a single dose of vismodegib 150 mg. Patients in the LF group took vismodegib 30 minutes after a meal consisting of 1 cup of cereal, 8 ounces of skim milk, one piece of toast with jam, apple juice, and a cup of coffee or tea; this meal provides approximately 520 calories. In part II, which lasted for 28 days, patients randomized to FO or HF in part I took vismodegib 150 mg daily after fasting; those randomized to LF took it 30 minutes after a recommended meal.

The 2 subsets of patients (before and after amendment) were analyzed separately and, as there were no significant differences between endpoints for the 2 subsets, pooled for analysis. The primary endpoints for part I were C_{max} and AUC_{0-168}, whereas secondary endpoints were T_{max} and T_{lag}. The coefficients of variation (CV) of C_{max}, AUC, and T_{max} were approximately 30% for each parameter in a single dose study with healthy volunteers (12). Assuming a CV of 30%, a sample size of 48 patients (12 in the LF group and 18 each in the HF and FO groups) would provide 85% and 80% power to detect a true ratio of geometric means of less than 67% or more than 150% (allowing for 15% inevaluable) with regard to the HF versus FO and LF versus FO comparisons, respectively, based on a 2-sided test at the 0.05 significance level. The study was not powered to detect a difference between the HF and LF arms. The primary endpoints for part II were C_{max} and AUC_{0-24}, whereas secondary endpoints were C_{trough} and T_{max}. Assuming a CV of 30%, a sample size of 48 patients (24 fasting and 24 fed) would provide very high power (over 95%) to detect a true ratio of geometric means of less than 67% or more than 150% (allowing for 15% inevaluable), based on a 2-sided test at the 0.05 significance level. At the time the study was designed, vismodegib seemed to be relatively well tolerated and did not seem to have a narrow therapeutic index, as there was no clear relationship between exposure and toxicity. Accordingly, the 67% and 150% thresholds were chosen rather than the more stringent thresholds recommended by FDA for bioequivalence (80% and 125%) because the investigators felt that the food effect would have to be more substantial to be clinically important.

Following the completion of part II, all patients took vismodegib after fasting for the remainder of the study. Toxicities were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0), and response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1; ref. 13).

Biosampling

Part I. On day 1, each patient received vismodegib in capsule form at a dose of 150 mg, followed by a 7-day observation period. Blood samples were collected at 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 24, 48, 120, and 168 hours after the dose. These samples were used to determine plasma concentrations of total vismodegib.

Published OnlineFirst April 3, 2013; DOI: 10.1158/1078-0432.CCR-12-3829

Part II. On day 1, patients began taking vismodegib 150 mg daily, either after fasting or after food. On day 14, each patient received vismodegib in capsule form at a dose of 150 mg, followed by a 24-hour observation period. Blood samples were collected at 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 24 hours after the dose. These samples were used to determine plasma concentrations of total vismodegib. The samples at 0.25, 1, 4, and 24 hours after the dose were also used to determine plasma concentrations of unbound vismodegib. The samples at 0, 8, and 24 hours after the dose were also used to determine plasma concentrations of AAG.

Bioanalysis of vismodegib in plasma

Total vismodegib plasma concentrations were determined by Tandem Labs using a validated solid-phase extraction liquid chromatography/tandem mass spectrometry (LC/MS-MS) method (12). Human plasma (K_2EDTA) samples containing vismodegib were analyzed in 200 μL aliquots. Vismodegib concentrations were calculated using a $1/x^2$ quadratic regression over a concentration range of 5.00 to 5,000 ng/mL, with vismodegib-d5 as an internal standard. The API 3000 was operated in the selected reaction monitoring mode under optimized conditions for the detection of vismodegib and vismodegib-d5 positive ions formed by electrospray ionization.

Selected plasma samples were assayed for unbound vismodegib, which was measured in dialysate from plasma samples that underwent equilibrium dialysis (QPS). Unbound plasma concentrations were determined using a LC/MS-MS method validated over a calibration curve range of 0.100 to 100 ng/mL (Tandem Labs; ref. 14).

Alpha-1-acid glycoprotein analytic methods

Concentrations of alpha-1-acid glycoprotein (AAG) in human K_2EDTA plasma were determined using a commercially available kit (Dade Behring Marburg) modified for assessment by 96-well ELISA.

Pharmacokinetic and statistical analyses

C_{max} was defined as the highest observed concentration. C_{trough} was defined as the concentration before the dose on day 14 during daily dosing. Individual patient AUC values were derived using noncompartmental analysis (WinNonlin 6.3, Pharsight) of total vismodegib concentration-time data. Exposure parameters (C_{max}, C_{trough}, and AUC) were log transformed for statistical analysis. Standard statistical software (STATA, version 12.1) was used to compare groups with respect to the various endpoints. For exposure parameters, a 2-sample *t* test with equal variances was used, and the ratios of geometric means were calculated. For T_{max} and T_{lag}, a Wilcoxon rank-sum test was conducted. Ninety-percent confidence intervals (CI) for the ratios of geometric means of the exposure parameters were obtained by back transformation. Multivariate regression analyses were conducted to explore the influence of covariates (age, gender, weight, mean AAG concentration) on the pharmacokinetic parameters and group comparisons with daily dosing. The allocation ratio was 1:1:2 in the postamendment phase to obtain an

Table 1. Characteristics of enrolled patients by cohort for a single dose of vismodegib 150 mg

		Fasting	High fat	Low fat
No. of subjects		23	20	20
Age (y), median (range)		53 (34–74)	57 (24–71)	64 (46–84)
Sex (%)	Male	8 (35)	9 (45)	14 (70)
	Female	15 (65)	11 (55)	6 (30)
Race (%)	White	16 (70)	17 (85)	16 (80)
	Black	6 (26)	3 (15)	2 (10)
	Hispanic	1 (4)	0	2 (10)
ECOG performance status (%)	0	16 (70)	12 (60)	11 (55)
	1	7 (31)	7 (35)	9 (45)
	2	0	1 (5)	0
Tumor type (%)	Colorectal	7 (30)	11 (55)	8 (40)
	Pancreatic	6 (26)	1 (5)	4 (20)
	Breast	2 (9)	1 (5)	0
	Biliary	0	2 (10)	1 (5)
	Renal cell	1 (4)	0	2 (10)
	Adenoid cystic	0	2 (10)	0
	Basal cell	1 (4)	1 (5)	0
	Chondrosarcoma	1 (4)	1 (5)	0
	Urothelial	1 (4)	0	1 (5)
	Other[a]	4 (17)	1 (5)	4 (20)

[a]A variety of tumor types with only a single patient enrolled.

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adequate number of patients in the LF arm. Similarly, patients in the HF arm took the drug fasted in part II after the amendment to maintain balance for the fasting versus fed comparisons during the 2 phases. When pooling the pre- and post-amendment data, it must be assumed that there was no systematic shift in the study population, as this could admit bias into the comparison of the LF versus FO arms. While this possibility can never be ruled out, comparisons of outcomes of patients pre- and postamendment did not suggest that this had occurred, as mean levels of pharmacokinetic parameters were very similar (data not shown).

Given the flat pharmacokinetic profile at steady state, concentrations of unbound vismodegib at the 4 timepoints were averaged for each patient, and used to confirm the expectation that total concentration is an appropriate surrogate for unbound concentration under daily dosing conditions. Unbound concentrations were not compared statistically between the fasting and fed groups due to the sparse sampling and variability associated with the measurement assay. Mean AAG concentrations (mean of concentrations at 0, 8, and 24 hours) were calculated for each patient and the fasting and fed groups were compared by a 2-sample *t* test with equal variances.

Results

Patient characteristics are described in Table 1. A total of 63 patients were enrolled. The most common tumor type was colorectal cancer (41%). Sixty patients were evaluable for the primary endpoints in the single dose part of the study: 22, 20, and 18 patients randomized to the FO, HF, and LF, respectively. These numbers exceeded the accrual goals of 18, 18, and 12 patients in the respective groups because 8 of these patients were not evaluable for the primary endpoints in the daily dosing part of the study. Fifty-two patients were evaluable for the primary endpoints in the daily dosing part of the study: 25 and 27 patients were randomized to the fasting and fed groups, respectively. During daily dosing before pharmacokinetic sampling, 17% of patients missed at least 1 dose of vismodegib and 28% had missing or incomplete food diaries.

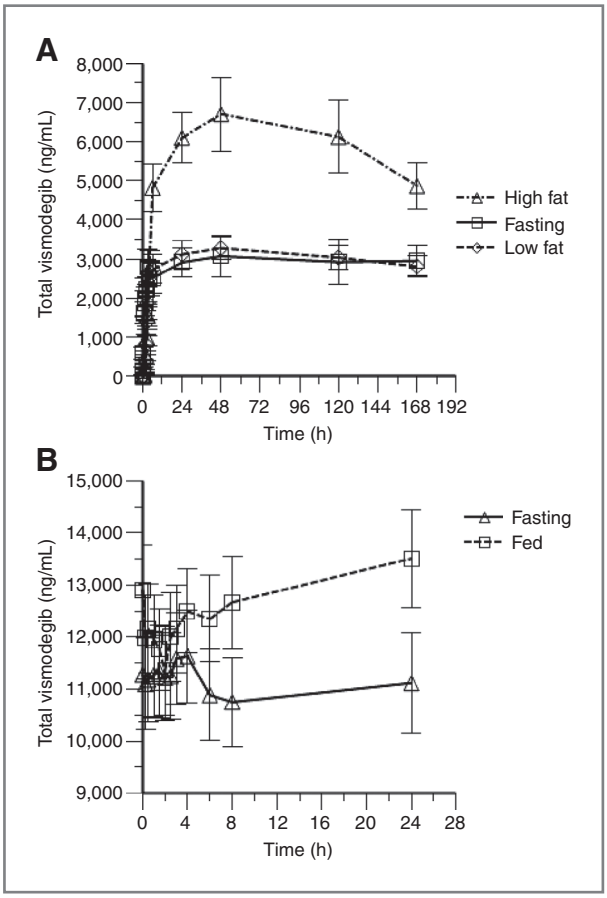

Figure 2. Mean ± SEM concentration-time profiles for vismodegib after a single dose of vismodegib 150 mg (A) and after 14 days of vismodegib 150 mg daily (B).

Mean concentration–time profiles for total vismodegib after a single dose and daily doses are presented in Fig. 2A and B, respectively. Mean pharmacokinetic parameters based on noncompartmental analysis after a single dose and daily doses are presented in Tables 2 and 3, respectively. Exposure parameters after a single dose and daily doses are

Table 2. Summary of pharmacokinetic parameters after a single dose of vismodegib 150 mg

	Fasting (FO) ($n = 22$)	High fat (HF) ($n = 20$)	Low fat (LF) ($n = 18$)		*P*	Ratio of geometric means (90% CI)
C_{max} (ng/mL)	3,244 (55)	5,666 (45)	3,511 (40)	HF/FO	0.003	1.75 (1.30, 2.34)
				LF/FO	0.65	1.08 (0.81, 1.44)
AUC_{0-168} (ng*h/mL)	416,635 (56)	723,822 (54)	466,566 (38)	HF/FO	0.008	1.74 (1.25, 2.42)
				LF/FO	0.51	1.12 (0.84, 1.49)
T_{max} (hours)	57 ± 62	44 ± 48	62 ± 57	HF/FO	0.83	—
				LF/FO	0.57	—
T_{lag} (hours)	0.11 ± 0.17	0.50 ± 0.29	0.58 ± 0.45	HF/FO	0.0001	—
				LF/FO	0.0001	—

NOTE: Exposure parameters (C_{max} and AUC) are reported as geometric mean (CV%), whereas T_{max} and T_{lag} are reported as mean ± SD.

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Table 3. Summary of pharmacokinetic parameters after 14 days of vismodegib 150 mg daily

	Fasting ($n = 25$)	Fed ($n = 27$)	*P*-value	Ratio of geometric means (90% CI)
C_{trough} (ng/mL)	10,493 (37)	12,171 (35)	0.17	1.16 (0.97–1.38)
C_{max} (ng/mL)	11,449 (37)	12,950 (34)	0.25	1.13 (0.95–1.35)
AUC_{0-24} (ng*h/mL)	238,740 (40)[a]	290,896 (35)[b]	0.096	1.22 (1.00–1.48)
T_{max} (hours)	6.7 ± 9.1	10.2 ± 10.3	0.27	—

NOTE: Exposure parameters (C_{trough}, C_{max}, and AUC) are reported as geometric mean (CV%), whereas T_{max} is reported as mean ± SD.
[a]$n = 22$.
[b]$n = 25$.

also depicted in box plots in Figs. 3A and B, and Figs. 3C, D, and E, respectively. Mean C_{max} and AUC_{0-168} after a single dose were higher in HF than in FO patients ($P = 0.003$ and 0.008, respectively); ratios of geometric means (90% CI) were 1.75 (1.30, 2.34) and 1.74 (1.25, 2.42), respectively. Mean C_{max} and AUC_{0-168} after a single dose were not significantly different in LF than in FO patients; ratios of geometric means (90% CI) were 1.08 (0.81, 1.44) and 1.12 (0.84, 1.49), respectively. There were no significant differences between groups for mean T_{max}. T_{lag} was significantly higher in HF and LF than in FO patients, although the absolute difference was relatively small. Mean C_{trough}, C_{max}, and AUC_{0-24} after daily dosing were similar in fasting and fed patients; ratios of geometric means (90% CI) were 1.16 (0.97–1.38), 1.13 (0.95–1.35), and 1.22 (1.00–1.48), respectively. T_{max} was not significantly different in fasting than in fed patients. Mean ± SD of unbound vismodegib concentrations after daily dosing were 79 ± 53 ng/mL and 103 ± 49 ng/mL in the fasting and fed groups, respectively. Mean ± SD of AAG concentrations after daily dosing were similar in the fasting and fed groups (34.6 ± 13.0 μmol/L vs. 33.6 ± 12.6 μmol/L; $P = 0.78$). Furthermore, the strength of the linear correlation between mean AAG concentration and exposure [log(AUC), log(C_{max}), log(C_{trough})] was similar in the fasting and fed groups. In multivariate regression analyses, no other covariates had a significant effect on exposure or fasting versus fed comparisons after adjusting for mean AAG concentration (data not shown).

Toxicity data for adverse events at least possibly attributable to vismodegib during daily dosing are presented in Table 4. The most common toxicities of any grade were fatigue (36%), anorexia (36%), dysgeusia (34%) and nausea (31%). Grade 3 toxicities included fatigue (5%), hyperkalemia (2%), hypophosphatemia (2%), and neutropenia (2%). There were no significant differences between the frequencies of toxicities in the fasting and fed groups by Fisher exact test.

Of 46 patients evaluable for response, there were no objective responses. Nine patients had stable disease for a median duration of 28 weeks (range: 8–152 weeks). The patient with the longest duration of stable disease (152 weeks) has BCC and remains on study.

Discussion

The results of this study show that there is no clinically relevant effect of prandial state on vismodegib pharmacokinetics. Following a single dose, a HF increased exposure to the drug as measured by mean C_{max} and AUC_{0-168}, compared with FO. Food also appears to have a small but significant impact on delaying absorption of the drug, as evidenced by the higher T_{lag}. However, even if patients were to consistently consume HFs before taking the drug, it is unlikely that there would be a relevant food effect with daily dosing. Vismodegib exposure may be influenced by food when AAG binding is not saturated in plasma (under single dose conditions), but with continuous dosing, steady-state vismodegib exposure is simply related to levels of AAG in plasma. Even when single dose exposure is increased, the increase is not a safety concern because plasma concentrations are at or below steady-state concentrations. This is due to accumulation of vismodegib with continuous dosing. As expected, the magnitude of change in exposure parameters was smaller after a LF compared with a HF, and was not statistically significant when compared with fasting.

During daily dosing, there were no statistically significant differences between fasting and fed groups with respect to steady state C_{trough}, C_{max}, or AUC_{0-24} with lower limits of the 90% confidence bounds exceeding 80% and upper limits ranging from 135% to 148%. Although the upper bounds of the 90% confidence intervals exceed 125%, this small food effect is very unlikely to be of clinical significance for a drug that does not have a narrow therapeutic index. Toxicities observed in the current study were similar to those previously reported (9, 15), and durable stable disease (more than 32 weeks) was only observed in a patient with BCC. Overall, the results of this study formed the basis for the instructions in the prescribing information that the drug may be taken either with or without food.

Although there were significant differences between groups with respect to certain demographic variables (age and sex), these did not have a significant effect on results of the study after adjusting for mean AAG concentration. This is consistent with a population pharmacokinetic analysis on 225 patients in 5 studies, which showed that AAG

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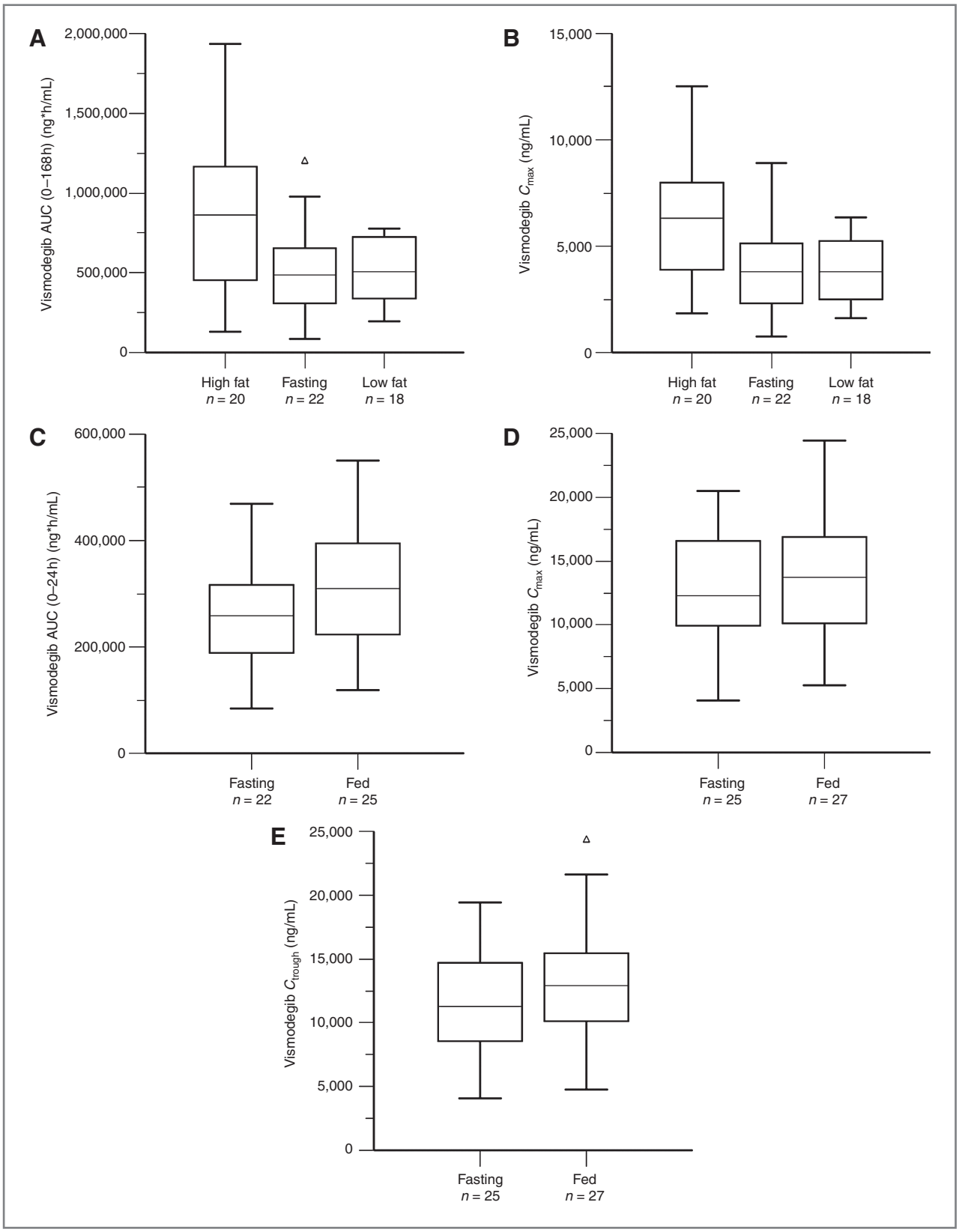

Figure 3. Box plots of $AUC_{0–168}$ (A) and C_{max} (B) after a single dose of vismodegib 150 mg, and of $AUC_{0–24}$ (C), C_{max} (D), and C_{trough} (E) after 14 days of vismodegib 150 mg daily. Triangles denote outliers.

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Table 4. Adverse events by group

	Fasting ($n = 31$)		Fed ($n = 30$)	
Adverse event	**Grade 3 (%)**	**All grades (%)**	**Grade 3 (%)**	**All grades (%)**
Alopecia		4 (13)		1 (3)
Anorexia		9 (29)		13 (43)
Diarrhea		4 (13)		3 (10)
Dizziness		3 (10)		2 (7)
Dysgeusia		8 (26)		13 (43)
Dyspnea		3 (10)		
Fatigue	2 (6)	11 (35)	1 (3)	11 (37)
Hyperglycemia		2 (6)		1 (3)
Hyperkalemia		1 (3)	1 (3)	1 (3)
Hypophosphatemia	1 (3)	3 (10)		
Myalgia		6 (19)		7 (23)
Nausea		10 (32)		9 (30)
Neutropenia			1 (3)	1 (3)
Vomiting		4 (13)		3 (10)
Weight loss		5 (16)		2 (7)

NOTE: Patients were included if they received at least one dose in the daily dosing part of the study. Events were included if at least possibly related to vismodegib and either at least grade 3 or present in at least 3 patients between the 2 groups. No drug-related adverse events above grade 3 were reported. There were no statistically significant differences between groups by Fisher exact test.

concentrations explain most (>70%) of the observed pharmacokinetic variability and that age, weight, sex, and creatinine clearance do not have a clinically meaningful effect on systemic exposure (16).

One can speculate that the absence of a food effect may be explained by the pharmacokinetics of the drug, although the true reasons are impossible to determine from this study. The long terminal half-life of vismodegib was observed in earlier studies and confirmed in the current study, as plasma concentrations at 168 hours were often close to C_{max}. Steady-state unbound drug concentrations were consistently less than 1% of total concentrations and were comparable between fasting and fed groups, consistent with previous evidence that the drug is highly bound to AAG (10). In contrast to vismodegib, oral anticancer drugs with significant food effects have shorter terminal half-lives (prescribing information for lapatinib, erlotinib, pazopanib, and nilotinib). Although absorption of vismodegib may be limited by solubility and enhanced by intake of a meal, this factor is likely negligible compared with protein-binding and slow metabolic elimination that more substantially impact exposure to total and unbound vismodegib.

The general design strategy of randomizing patients to 3 groups (FO, HF, and LF) for single dosing followed by 2 groups (fasting and fed) for daily dosing is one that could easily be applied to other oral anticancer drugs. For the fed group with daily dosing, the healthy breakfast was chosen because it was not practical to require patients to consume a high-fat, high-calorie breakfast daily for 14 days. The recommended healthy breakfast chosen for this study is expected to be representative of the real-life situation under which patients may take vismodegib on a daily basis. While a crossover design randomizing half the patients to fasting followed by fed and half the patients to fed followed by fasting for multiple dosing would be more efficient, this design is not feasible for drugs with a long terminal half-life and would not decrease the sample size needed for single dose pharmacokinetic endpoints. In the current study, 63 patients were enrolled but only 47 were evaluable for AUC_{0-24} with daily dosing, suggesting that an inevaluable rate as high as 25% should be factored into sample size calculations.

There are a few limitations to the current study. First, nonadherence to the assigned prandial state is a potential confounding factor. Although medication and food diaries were requested from patients during this study, they were either not returned or incomplete in a substantial minority of patients, making an accurate assessment of adherence difficult. Second, nonadherence to the rigorous pharmacokinetic sampling program led to missing samples at specific time points for some patients and limited the sample sizes available for statistical comparisons. For example, 4 patients did not return for pharmacokinetic sample collection on day 15 of daily dosing (24 hours after the day 14 dose), making it impossible to calculate a

steady-state AUC_{0-24}. Finally, the validity of our conclusions rests on the assumption that the subset of evaluable patients with advanced solid tumors is representative of patients for whom the drug is indicated.

In conclusion, although there are statistically significant effects of food on vismodegib pharmacokinetics after a single dose, these findings do not affect vismodegib exposure with daily dosing. The drug can be administered with or without food for standard use and in ongoing/future clinical trials, a fact that makes drug administration convenient for patients, physicians, and investigators alike. Furthermore, there does not appear to be any risk of food-induced serious toxicity due to an inadvertent increase in exposure.

Disclosure of Potential Conflicts of Interest

M.J. Ratain is a consultant/advisory board member of Genentech. No potential conflicts of interest were disclosed by the other authors.

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Grant Support

The study was sponsored by the Cancer Therapy Evaluation Program and supported by NCI grant 5U01-CA69852-12 (Principal investigator: M.J. Ratain). M.R. Sharma was supported by award number K12CA139160 from the National Cancer Institute.

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Received December 20, 2012; revised March 18, 2013; accepted March 25, 2013; published OnlineFirst April 3, 2013.

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Published OnlineFirst April 3, 2013; DOI: 10.1158/1078-0432.CCR-12-3829

Clinical Cancer Research

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Clin Cancer Res Published OnlineFirst April 3, 2013.