request of Cubist Pharmaceuticals, we evaluated daptomycin exposure-response relationships for safety and efficacy end points. Prior to conducting these analyses, a definition of creatine phosphokinase (CPK) elevation was agreed on with sponsor scientists, and initial exposure-response analyses for CPK elevation were presented at the aforementioned Food and Drug Administration Anti-Infective Drugs Advisory Committee meeting.

Since that time, subsequent analyses with altered definitions of CPK elevation were conducted at the sponsor's request. These additional analyses continued to demonstrate significant relationships between daptomycin exposure and CPK elevation, indicating the robustness of the findings. The probability of CPK elevation was 50% and 2.9% for daptomycin trough concentrations (C_{min}) $\geqslant$24.3 mg/L and <24.3 mg/L, respectively [2], a finding that we believe to be clinically useful in assessing patient risk-benefit.

Donovan et al, in their letter [3], assert that the 24.3 mg/L C_{min} threshold value identified lacks sensitivity. To support this point, they calculate a positive predictive value of 50% (which, although confusing, coincidently provides the same value as that calculated for sensitivity). On the basis of the daptomycin C_{min} threshold value of 24.3 mg/L and the occurrence of CPK elevation, the sensitivity, specificity, and positive and negative predictive values were 50%, 97.1%, 50%, and 97.1%, respectively.

There are daptomycin-linked and non–daptomycin-linked CPK elevations. As described above, the probability of CPK elevation is 2.9% if the C_{min} is below the threshold of 24.3 mg/L and 50% if the C_{min} is above it [2]. There will always be patient-specific variability where CPK elevation and subsequent adverse musculoskeletal effects may not manifest even with a C_{min} in excess of the threshold. A useful analogy involves aminoglycosides and nephrotoxicity. Not all patients with elevated aminoglycoside exposures develop nephrotoxicity, yet clinicians rightly monitor aminoglycoside concentrations regularly as part of a patient risk-benefit assessment. We contend that knowing whether a patient has a daptomycin C_{min} above the threshold, which is associated with a >17-fold (50% vs 2.9%) increase in the likelihood of a potential harbinger of toxicity, is clinically helpful.

We are confused about the authors' implication that we recommend daptomycin C_{min} monitoring in all circumstances. As discussed elsewhere [2], given the cost of chemical assays and the availability of low cost serum CPK assays, daptomycin C_{min} monitoring may be indicated when a CPK elevation of >1000 IU/L (~5 times the upper limit of normal) with clinical signs of adverse muscle effects or >2000 IU/L ($\geqslant$10 times the upper limit of normal) without clinical signs has of adverse muscle effects occurred and the clinician believes that continuing daptomycin therapy is imperative. Otherwise, we recommended more intensive CPK monitoring.

As described elsewhere [2], we used Monte Carlo simulation to evaluate the impact of administering daptomycin on the basis of total or lean body weight in patients $\geqslant$111 kg. These analyses demonstrated that the probability of both attaining a C_{min} value in excess of the threshold and underdosing (as assessed by comparing area-under-the-curve distributions) are minimized when daptomycin is administered on the basis of lean body weight in obese patients. As we explicitly stated [2], the risks versus benefits of such a therapeutic approach need to be weighed by the clinician. Donovan et al [3] evaluated the results of this analysis in the context of 2 of the reported 6 patients with CPK elevation, 1 of whom weighed 111 kg (C_{min}, 3.8 mg/L) and the other of whom weighed 80 kg (C_{min}, 24.3 mg/L) [3]. Later, the authors critique us for not discussing "the impact of drug clearance on C_{min}" when evaluating dosing strategies for obese patients [2]. We are unsure of the point the authors are making by highlighting these 2 patients and their later critique regarding clearance. We encourage the authors to consider the probabilistic nature of the results of the Monte Carlo simulations rather than pointing to individual cases. We conducted the simulations by incorporating the actual distributions of pharmacokinetic parameters observed in patients <111 kg and $\geqslant$111 kg. The impact of drug clearance on C_{min} was, therefore, explicitly considered. We fully stand by our analyses and our conclusions, which support periodic monitoring of daptomycin C_{min} in a small subset of patients.

Acknowledgments

Potential conflicts of interest. G.L.D. has received consulting fees and/or grants from Cubist, Forrest Laboratories, and Novexel. P.G.A., S.M.B., and C.M.R. have received consulting fees and/or grants from Achaogen, Cempra, Cerexa, Cubist, The Medicines Company, Nabriva, Novartis, Pfizer, and PolyMedix.

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Clinical Infectious Diseases 2010; 51(8):989–990

1058-4838/2010/5108-0024$15.00
DOI: 10.1086/656441

Coronary Aging in HIV-Infected Patients

To the Editor—We read with interest the report by Guaraldi et al [1] on coro-

Table 1. Characteristics of Human Immunodeficiency Virus (HIV)–Infected Persons with Increased Coronary Aging, Compared with HIV-Infected Individuals with Expected and/or Decreased Coronary Aging

Variable	Overall	Coronary age		OR (95% CI)	*P*
		Increased	Expected or Decreased		
Population	223	67 (30)	156 (70)		
Age, years	43 (36–50)	49 (43–54)	41 (33–46)	1.1 (1.1–1.1)	<.001
Male sex	213 (96)	63 (94)	150 (96)	0.6 (0.2–2.3)	.49
Ethnicity					
White	110 (49)	41 (61)	69 (44)	1.7 (0.8–3.3)	.14
Black	52 (23)	10 (15)	42 (27)	0.7 (0.3–1.6)	.38
Other	61 (28)	16 (24)	45 (29)	1.0 (Referent)	
BMI, mean value (IQR)	26.7 (24.2–29.5)	26.8 (23.9–29.2)	26.7 (24.3–29.8)	1.0 (0.9–1.1)	.86
Waist-hip ratio, mean value (IQR)	1.01 (0.96–1.04)	1.01 (0.96–1.05)	1.00 (0.96–1.04)	3.8 (0.4–36.0)	.25
Percentage body fat, mean % (IQR)	26 (23–30)	28.2 (24.3–33)	26 (22.5–29.3)	1.1 (1.0–1.1)	.006
Tobacco use					
Ever	111 (50)	36 (54)	75 (48)	1.3 (0.7–2.2)	.44
Duration of use, mean years (IQR)	12 (5–20)	18.5 (10–25)	10 (5–18)	1.1 (1.0–1.1)	.001
Hyperglycemia[a] (>110 mg/dL)	21 (9)	9 (13)	12 (8)	1.9 (0.7–4.7)	.18
Hypercholesterolemia[a] (>200 mg/dL)	71 (32)	27 (40)	44 (28)	1.7 (0.9–3.1)	.08
Low HDL[a] (<40 for men and <50 mg/dl women)	102 (46)	30 (45)	72 (46)	0.9 (0.5–1.7)	.85
Hypertriglyceridemia[a] (>150 mg/dL)	106 (48)	39 (58)	67 (43)	1.9 (1.0–3.3)	.04
High LDL (>160 mg/dL)	25 (11)	10 (15)	15 (10)	1.6 (0.7–3.9)	.25
Anti-lipid medication	70 (31)	33 (49)	37 (24)	3.1 (1.7–5.7)	<.001
Diabetes mellitus[b]	14 (6)	7 (10)	7 (5)	2.5 (0.8–7.4)	.10
Hypertension[b]	66 (30)	30 (45)	36 (23)	2.7 (1.5–5.0)	.001
Metabolic syndrome	50 (23)	22 (33)	28 (18)	2.2 (1.2–4.3)	.02
Fatty liver disease by CT	29 (13)	17 (26)	12 (8)	4.1 (1.8–9.3)	<.001
C-reactive protein (>0.5 mg/dL)	31 (14)	14 (21)	17 (11)	2.2 (1.0–4.7)	.05
ESR (>20 mm/h)	53 (24)	16 (24)	37 (24)	1.0 (0.5–1.9)	.98
HIV infection duration, mean years (IQR)	12 (5–19)	17 (10–22)	8.5 (4.3–16.5)	1.1 (1.0–1.1)	<.001
$CD4^+$ cell count, mean cells/mm (IQR)					
Current	586 (393–733)	591 (328–816)	585 (417–712)	1.01[c](0.95–1.06)	.86
Nadir	260 (144–368)	240 (96–345)	265.5 (160.5–374)	0.90[c] (0.82–0.99)	.04
HIV RNA level <50 copies/mL	157 (70)	49 (73)	108 (69)	1.2 (0.6–2.3)	.56
Current HAART use	185 (83)	61 (91)	124 (79)	2.6 (1.0–6.6)	.04
Abacavir use					
Current	42 (19)	17 (25)	25 (16)	1.8 (0.9–3.6)	.10
Ever	78 (35)	33 (49)	45 (29)	2.4 (1.3–4.3)	.004
NRTI, mean months of use (IQR)	77 (20–149)	139 (66.1–181.5)	54.4 (11.9–130.5)	1.1 (1.1–1.2)	<.001
NNRTI, mean months of use (IQR)	17 (0–51)	31.5 (0–60)	13.1 (0–43.9)	1.1 (1.0–1.2)	.03
PI, mean months of use (IQR)	26 (0–75)	46.7 (3.3–104)	8.3 (0–70)	1.1 (1.0–1.2)	.009

NOTE. Data are no. (%) of subjects, unless otherwise indicated. BMI, body mass index, calculated as the weight in kilograms divided by the square of height in meters; CI, confidence interval; ESR, erythrocyte sedimentation rate; HAART, highly active antiretroviral therapy; HDL, high density lipoprotein; IQR, interquartile range; LDL, low density lipoprotein; NRTI, nucleoside reverse-transcriptase inhibitor; NNRTI, non-nucleoside reverse-transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor.

[a] Based on the definitions from the National Cholesterol Education Program [4].

[b] Diagnosis based on use of medication for the condition.

[c] OR calculated per 50 cells/mm^3.

nary aging among human immunodeficiency virus (HIV)–infected patients. It has been hypothesized that the increased rates of several non–AIDS-defining conditions, including cardiovascular disease, may be attributable in part to accelerated aging in this population.

We recently performed a cross-sectional study among HIV-infected adults to evaluate the prevalence of and factors associated with subclinical coronary atherosclerosis as detected by computed tomography (CT) for coronary artery calcium (CAC). Patients also underwent CT for detection of fatty liver disease [2]. Results of this original study were re-evaluated for coronary age on the basis of published sex- and race-specific polynomial equations [3], and differences between the chronologic and coronary age were computed. Logistic regression models were performed for factors associated with increased, compared with expected or decreased, coronary aging. In addition, linear regression models were used to examine factors associated with the degree of coronary aging among those with CAC (Stata software, version 10; Stata).

We evaluated 223 HIV-infected adults with a median age of 43 years (interquartile range [IQR], 36–50 years). Of these subjects, 96% were male, 49% were white, 23% were black, and 28% were of other

races. Median $CD4^+$ cell count was 586 cells/mm^3 (IQR, 393–733 cells/mm^3), and 83% were receiving antiretroviral medications. Seventy-five patients had a positive CAC score (defined as >0). Increased coronary age was observed in 67 patients (89% of patients with CAC and 30% of the total study cohort). The median increase in vascular age was 18 years (IQR, 13–29 years) higher than the chronological age.

We compared those with and without increased coronary age and found that accelerated coronary aging was univariately associated with chronologic age, hypertension, duration of tobacco use, fatty liver disease, metabolic syndrome, percentage of body fat, hypertriglyceridemia, use of an antilipid medication, low $CD4^+$ cell count nadir, duration of HIV infection, and duration of antiretroviral use ($P < .05$), with a trend for elevated C-reactive protein (CRP) level (Table 1). In the final multivariate model, fatty liver disease (odds ratio [OR], 4.4; $P = .001$) and increasing chronological age (OR, 2.6 per 10 years; $P < .001$) were significantly associated with increased coronary age, with a trend for elevated CRP level (OR, 2.3; $P = .05$).

In our linear regression modeling for predictors of increasing coronary age among those with CAC, we found that both higher current $CD4^+$ cell count (β 0.53 per 50 cells/mm^3; 95% confidence interval [CI], 0.05–1.01 cells/mm^3; $P = .03$), and higher nadir $CD4^+$ cell counts (β 1.73 per 50 cells/mm^3; 95% CI, 0.86–2.60 cells/mm^3; $P < .001$) were univariately associated with increasing coronary aging; the latter is shown in Figure 1. There was no association between coronary aging with the difference between nadir and current $CD4^+$ cell counts ($P = .73$). $CD4^+$ cell count nadir and current counts were highly correlated ($r = 0.46$; $P < .001$). In separate final multivariate models, both nadir (β 1.29; $P = .004$) and current $CD4^+$ cell counts (β 0.50; $P = .03$) remained significantly associated with increasing coronary age.

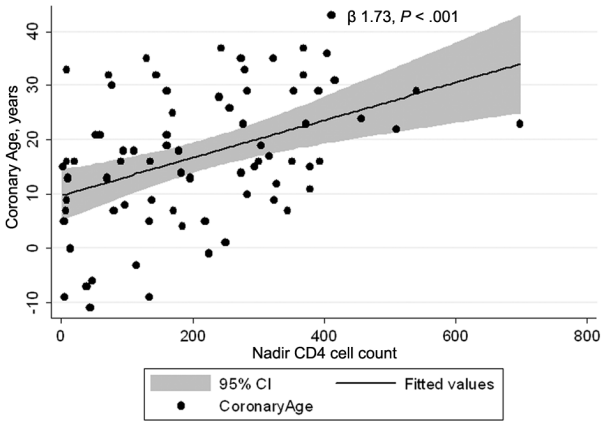

Figure 1. Univariate linear regression associations between coronary age and nadir $CD4^+$ cell count. CI, confidence interval.

Overall, our results confirm many of the findings by Guaraldi et al [1]. In addition, our study extends present data by showing that fatty liver disease—and perhaps elevated inflammatory markers (eg, CRP level)—may be related to the development of increased vascular aging. The precise relationship of these factors is unclear because of the cross-sectional design of the study but may represent markers of an underlying systemic pro-atherogenic state that results in accelerated vascular aging.

We found that higher current and nadir $CD4^+$ cell counts were associated with greater increases in coronary aging in our linear regression models. In the final model, nadir $CD4^+$ cell count in our study was particularly associated with coronary aging. Of note, our study was conducted in a cohort of individuals who had received early diagnosis and treatment and, in general, did not experience low nadir $CD4^+$ cell counts. Although higher $CD4^+$ cell counts were not associated with the development of CAC in either study, once atherosclerosis is present, more robust counts may lead to T-cell mediated atherogenesis, faster progression of lesions, and accelerated vascular aging. As noted by Guaraldi et al [1], the exact mechanism is currently unknown.

Overall, these data suggest that accelerated vascular aging is common among HIV-infected persons. To reduce the impact of cardiovascular disease in this population, additional data on the pathogenesis of increasing vascular age—and ultimately therapeutic strategies to slow aging—are needed.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

Financial support. The Infectious Disease Clinical Research Program, a Department of Defense program executed through the Uniformed Services University of the Health Sciences, and the National Institute of Allergy and Infectious Diseases, National Institutes of Health, under Inter-Agency Agreement Y1-AI-5072.

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Clinical Infectious Diseases 2010; 51(8):990–993
 1058-4838/2010/5108-0025$15.00
DOI: 10.1086/656442

Fatal Cases of Pandemic (H1N1) 2009 Influenza despite Their Early Antiviral Treatment in Japan

Neuraminidase inhibitors, including oseltamivir and zanamivir, are currently used for treatment of influenza infections. These drugs are also considered to be effective against pandemic (H1N1) 2009 influenza. It is recommended that antiviral drugs should be given especially to patients who are at increased risk of developing complications [1]. In Japan, neuraminidase inhibitors have been widely used, even for seasonal influenza and most cases of pandemic (H1N1) 2009 influenza. We assessed the timing of the antiviral treatment and the patient outcome by comparing fatal cases and severe but nonfatal cases of pandemic (H1N1) 2009 influenza in Japan. During the pandemic, fatal and severe cases were reported to the Ministry of Health, Labour, and Welfare (MHLW). At the same time, the clinical manifestation and clinical course of these cases were posted on the MHLW Web site. A severe case was defined as a patient who required admission to the intensive care unit (ICU) or who required mechanical ventilation. Both fatal and severe cases were confirmed as pandemic (H1N1) 2009 influenza by use of real-time reverse-transcription polymerase chain reaction. We included all 198 fatal cases that were reported from 15 August 2009 (when the first case was reported) through 15 March 2010. We also included 56 severe cases that were reported from 5 August through 11 October 2009, because the MHLW stopped reporting severe cases in mid-October.

Of 198 fatal cases, 158 (80%) were reported to have received antiviral treatment; of 56 severe cases, 42 (75%) were reported to have received antiviral treatment. We evaluated the timing of the antiviral treatment after the onset of symptoms between the 2 groups. As a result, the median time from the onset of illness to the initiation of antiviral drugs was 1 day for both groups, with a range of 0–18 days for fatal cases and 0–7 days for severe cases. Furthermore, 104 (66%) of 158 fatal cases and 30 (71%) of 42 severe cases have received antiviral drugs on day 0 or 1 after their onset of symptoms (Figure 1).

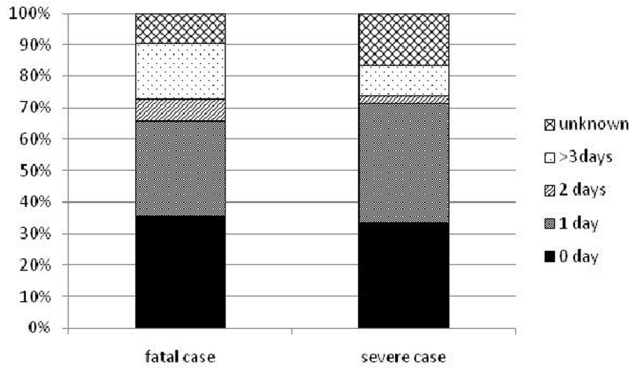

Figure 1. Duration between onset of illness and initiation of antiviral drugs. Both fatal and severe cases were confirmed as pandemic (H1N1) 2009 influenza by use of real-time reverse-transcription polymerase chain reaction. We included 158 fatal cases in patients who received antiviral treatment among all 198 fatal cases that were reported from 15 August 2009 (when the first case was reported) through 15 March 2010. We also included 42 severe cases in patients who received antiviral treatment among all 56 severe cases that were reported from 5 August through 11 October 2009, because the Ministry of Health, Labour, and Welfare stopped reporting severe cases in mid-October.

Available evidence suggests that early treatment with oseltamivir for patients with pandemic (H1N1) 2009 virus infection may reduce the duration of hospitalization [2] and the risk of progression to severe disease requiring ICU admission or resulting in death [3–5]. In Japan, during the early stage of illness, patients with symptoms of influenza-like illness tend to visit health clinics and start antiviral treatment promptly. We could not see any significant difference between fatal and severe cases in the timing of antiviral treatment after symptom onset. In Japan, where most of the patients had access to early antiviral treatment and hospital care, most of the fatal cases had also received early antiviral treatment. In other countries, those patients who received early antiviral treatment might also have received early hospital care, which can be a potential bias in assessing the impact of antiviral treatment. Although our observational data do not provide direct evidence of the effectiveness of antiviral treatment, our data clearly indicate that some severe cases had fatal outcomes despite their early treatment with antiviral drugs. More data are needed to define the exact impact of early antiviral treatment on outcome of influenza infections, including pandemic (H1N1) 2009 influenza.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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