MAJOR ARTICLE

The Effect of Statins on Mortality in Patients with Bacteremia

A. P. Liappis,[1,2] V. L. Kan,[1,2] C. G. Rochester,[3] and G. L. Simon[1,2]

[1]Division of Infectious Diseases, Department of Medicine, Veterans' Affairs Medical Center, and [2]George Washington University Medical Center, Washington, DC; [3]Division of Biometrics III, Center for Drug Evaluation and Research, United States Food and Drug Administration, Rockville, Maryland

The statins, inhibitors of 3-hydroxy-3-methylglutaryl–coenzyme A reductase, act to regulate the biosynthesis of cholesterol. Statins also deplete nonsterol cholesterol precursors, the isoprenoids, which are necessary for prenylation of critical membrane proteins that regulate cellular communication, including the inflammatory response. In a retrospective review of 388 bacteremic infections due to aerobic gram-negative bacilli and *Staphylococcus aureus,* there was a significant reduction in both overall (6% vs. 28%; $P = .002$) and attributable (3% vs. 20%; $P = .010$) mortality among patients taking statins compared with patients not taking statins. This reduction in mortality persisted in a multivariate analysis (odds ratio, 7.6; 95% confidence interval, 1.01–57.5). Among the statin group, diabetes, hypertension, and coronary artery disease were more prevalent ($P < .001$), and there were more skin and soft tissue infections identified as sources of bacteremia ($P = .008$). These data suggest a potential clinical role of statins in bacteremic infection; however, the mechanism by which mortality is reduced remains undefined.

Cholesterol metabolism is a highly regulated process that uses a complex system of enzymatic feedback mechanisms. These mechanisms balance dietary uptake of cholesterol with de novo hepatic biosynthesis and regulate its transport to selected peripheral organs. 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase is the rate-limiting enzymatic step in cholesterol biosynthesis [1]. The drugs that competitively inhibit HMG-CoA reductase and that reduce cholesterol biosynthesis are collectively known as "statins." Statins have been shown to play an important role in the treatment of hyperlipidemia and in reducing the risk of coronary artery disease [2, 3].

The role of inflammation in destabilizing atherosclerotic arterial plaques has become an active area of cardiovascular research [4, 5]. Components of the inflammatory process, including lipid-laden macrophages, augment plaque rupture, cause subsequent thrombosis, and lead to myocardial ischemia and infarction. Both in vitro and animal studies have proposed that statins may play a role in reducing the local inflammatory reaction within atherosclerotic plaques through direct, non–lipid-lowering effects [6, 7].

The clinical anti-inflammatory potential of statins in noncardiovascular conditions has not been defined. It has recently been reported that mice treated with lovastatin experience a decrease in leukocyte migration into the lung parenchyma after intranasal instillation of endotoxin, and there is a measurable decrease in the production of TNF at higher statin doses [8].

The mortality due to bacteremic infections is highly dependent on the inflammatory response and cytokine production. We have evaluated clinical outcomes in bacteremic infection among patients receiving statins to assess whether these drugs might have a role in altering the host response to bloodstream infection. This retrospective analysis compares the mortality and clinical and laboratory findings among patients taking

Received 15 November 2000; revised 8 May 2001; electronically published 20 September 2001.

Reprints or correspondence: Dr. Gary L. Simon, George Washington University Medical Center, Div. of Infectious Diseases, 2150 Pennsylvania Ave., Northwest, Suite 5-411, Washington, DC 20037 (domgls@gwumc.edu).

Clinical Infectious Diseases 2001; 33:1352–7

1058-4838/2001/3308-0013$03.00

statins with those of patients who where not receiving statins at the time of their bacteremic episode.

METHODS

We reviewed the clinical records of patients with bacteremic infection due to aerobic gram-negative bacilli and *Staphylococcus aureus* organisms at the Veterans' Affairs Medical Center (VAMC) in Washington, DC, during September 1995 through April 2000. Isolates considered potential skin contaminants, such as diphtheroids or coagulase-negative staphylococci, were not included in this study. *S. aureus* microbial isolates were included to represent gram-positive infection. There were relatively few streptococcal isolates, and many of these were from patients with α-hemolytic streptococcal endocarditis, in whom the pathophysiological changes due to the bacteremia are dissimilar from the sudden cytokine release that may be seen in other bacteremic conditions. We chose not to include anaerobic organisms in our study population, because they were underrepresented among patients taking statins and might have contributed disproportionately to the mortality of the nonstatin group.

Only those patients taking a statin at the time of admission and who continued their statin throughout the course of hospitalization were included in the statin group. All statins used at the VAMC during the study period were evaluated. We did not address the length of statin treatment, outpatient compliance, or efficacy of lipid lowering in this retrospective review.

By use of the computerized medical records available at the VAMC, clinical data from the time of positive results of blood culture were collected. Data collected included age, vital signs, intensive care unit (ICU) stay, concurrent medications, laboratory data, underlying medical conditions, and probable source of bacteremia. Hospital-acquired bacteremia was defined as that which occurred >48 h after the date of admission. Sources of information included the admission history and physical examination, medication orders, written notes, discharge summaries, and available corroborating radiological and laboratory data.

Overall mortality was defined as death that occurred sometime during the course of hospitalization from any cause. Mortality attributable to the bacteremic episode was based on the circumstances of death, as determined by review of the available recorded observations made by the attendant physicians as well as septic parameters that were gleaned from the medical charts.

Statistical analysis was done using Fisher's exact test and a multivariate logistic regression model (StrataCorp 1997, Strata statistical software, release 5.0)

RESULTS

A total of 388 bacteremic episodes from the VAMC were collected for analyses. These included 243 episodes (63%) of aerobic gram-negative bacteremia and 145 episodes (37%) of *S. aureus* bacteremia. Among the patients with bloodstream infections, a total of 35 patients (9%) were taking a statin drug, with 20 patients in the gram-negative bacteremia group and 15 in the *S. aureus* bacteremia group.

Simvastatin was the most common statin prescribed: 14 of 15 patients in the *S. aureus* bacteremia group (with the 1 remaining patient taking lovastatin) and 13 of 20 in the gram-negative bacteremia group were taking simavastitin. Fluvastatin accounted for 5 of the 20 statins prescribed for patients with gram-negative bacteremia, whereas atorvastatin and pravastatin were each given to 1 patient in the gram-negative bacteremia group.

Patients with bacteremia were predominantly male (386 [99.5%] of 388 patients), which reflects the VAMC population, and had a mean age ($\pm$SD) of 63 $\pm$ 13 years (table 1). Other than a low albumin level and reduced platelet count among the patients who did not receive statins, the 2 groups did not differ with regard to any laboratory parameters.

Underlying medical conditions are summarized in table 2. The statin group had a higher incidence of diabetes, hypertension, and coronary artery disease ($P < .001$). The mortality rates for

Table 1. Demographic characteristics and laboratory data at time of positive blood culture result among hospitalized patients with bacteremia.

Characteristic (abnormal level)	Patients who received statins (n = 35)	Patients who did not receive statins (n = 353)
Mean age, years	63.7	63.2
Male, no.	35	351
Creatinine (>1.5 mg/dL)	18/32 (56)	177/329 (54)
Glucose (>120 mg/dL)	19/32 (59)	156/330 (47)
Bicarbonate (<21 m*M*)	12/32 (38)	116/330 (35)
Albumin (<3.7 g/L)[a]	5/11 (45)	134/155 (86)
Prothrombin time (>11.7 s)	9/12 (75)	96/119 (81)
Platelet count (<152,000 platelets/mm^3)[b]	5/32 (16)	120/337 (36)
Hematocrit (<38.5 g/dL)	29/32 (91)	284/339 (84)
Total WBC count (>9500 cells/mm^3)	22/32 (69)	215/339 (63)
Calcium (<8.9 mg/dL)	15/19 (79)	157/240 (65)
Total cholesterol (>200 mg/dL)[c]	9/26 (35)	29/140 (21)
High-density lipoprotein (<32 mg/dL)[c]	5/12 (42)	8/40 (20)

NOTE. Data are no. of patients with abnormal level/total no. of patients (%), unless otherwise indicated. Denominators vary because of availability of data at the time of positive blood culture result.

[a] $P = .006$, by means of 2-tailed Fisher's exact test.

[b] $P = .021$, by means of 2-tailed Fisher's exact test.

[c] Most recent values collected within 1 year preceding bacteremic episode.

all patients were highest among those with a history of cirrhosis or chronic hepatitis (40%) or congestive heart failure (33%).

For both groups, the source of the bacteremic infection was unknown for approximately one-fourth of the patients (table 3). Urinary tract infections, which accounted for one-fourth of the infections, were the most frequently identified source of bacteremia in both groups. There were more pulmonary infections among patients who did not receive statin, and there were significantly more skin and soft tissue infections among patients who took statin drugs.

A review of concurrent medications revealed that those patients who were receiving statins were more likely to be receiving aspirin, β-blockers, insulin, diuretics, and calcium channel blockers. As noted below, none of these additional drugs were shown to have had a statistically significant effect in reducing mortality rates in a multivariate analysis. There were no significant differences between patients who did and those who did not receive statins with regard to administration of angiotensin-converting enzyme (ACE) inhibitors, digoxin, warfarin sodium, oral hypoglycemic agents, corticosteroids, or erythropoietin.

Overall hospital mortality rates (table 4) were reduced among patients taking statins, with a mortality rate of 6% (2 of 35 patients), compared with 28% (100 of 353 patients) for the patients who did not receive statins ($P = .002$). Mortality rates directly attributable to the infection were also lower: 3% (1 of 35 patients) for patients who took statins compared with 20% (70 of 353 patients) for patients who did not receive statins ($P = .010$). When analyzed separately, there was a trend toward reduced mortality among those patients who took statins for both gram-negative bacteremia and *S. aureus* bacteremia, but these findings did not reach statistical significance because of the relatively small numbers in each group.

As expected, patients with hospital-acquired infection had a higher mortality rate (40 [27] of 147 patients) than did those with community-acquired bacteremia (31 [14%] of 221 patients; $P = .012$). Similarly, the mortality rate for patients in the ICU (26 [36%] of 73 patients) was higher than that for those patients who received routine ward care (46 [15%] of 315 patients; $P < .001$). However, admission to the ICU while the patients had bacteremia was not significantly different between the patients who did (6 [17.1%] of 35 patients) and did not receive statins (68 [19.3%] of 353 patients). This observed increase in mortality rates among patients with hospital-acquired bacteremia or ICU stay was seen only in patients who did not take statins. There were no deaths among patients with hospital-acquired bacteremia or among patients in the ICU who were receiving statins.

There were no significant differences in attributable mortality among the various gram-negative microbial isolates (table 5). Among patients with *S. aureus* bacteremia, no statistical differences in attributable mortality were noted between patients

Table 2. Underlying medical diagnoses at time of bacteremia among hospitalized patients with bacteremia.

Diagnosis	Frequency for all patients, % (n = 388)	No. of patients who: Received statin (n = 35)	No. of patients who: Did not receive statin (n = 353)	P[a]
Chronic renal insufficiency	29.1	2	30	NS
Hemodialysis or end-stage renal disease	20.9	10	71	NS
Malignancy	32.2	10	115	NS
Neutropenia	2.8	0	11	NS
Diabetes mellitus	33.8	24	107	<.001
Hypertension	46.1	28	151	<.001
Coronary artery disease	21.4	15	68	<.001
Cirrhosis or chronic hepatitis	5.9	0	23	NS
Peripheral vascular disease	11.6	8	37	NS
HIV or AIDS	8.5	0	33	NS
Cerebral vascular disease	14.9	9	49	NS
Seizure disorder	8.8	3	31	NS
Chronic obstructive pulmonary disease or chronic lung disease	11.1	3	40	NS
Polysubstance abuse	16.2	0	63	.006
Congestive heart failure	10.3	5	35	NS

NOTE. Several patients had >1 underlying disease at time of bacteremia.

[a] Analyzed using 2-tailed Fisher's exact test.

Table 3. Sources of bacteremia and related attributable deaths among hospitalized patients with bacteremia.

Source	Frequency, % (n = 388)	Patients who received statins (n = 35)		Patients who did not receive statins (n = 353)		P[a]
		No.	No. of deaths	No.	No. of deaths	
Pleuropulmonary	9.0	0		35	13	.059
Urinary tract	27.3	9	1	97	20	NS
Intravenous catheter	12.9	4		46	5	NS
Skin or soft tissue	9.0	8		27	3	.008
Peritoneal	2.3	0		9	1	NS
Hemodialysis access	3.9	3		12	2	NS
Biliary or gastrointestinal tract	4.1	1		15	4	NS
Bone or joint	1.3	1		4		NS
Endocarditis	2.3	0		9	1	NS
Unknown	27.8	9		99	21	NS

[a] Analyzed with 2-tailed Fisher's exact test.

with methicillin-sensitive *S. aureus* and those with methicillin-resistant *S. aureus*.

Multivariate analysis of age, comorbid conditions, concurrent medications, site of infection, vital signs, ICU stay, and laboratory data revealed that only statins were associated with a decreased mortality rate (OR, 7.63; 95% CI, 1.01–57.5). The use of ACE inhibitors was associated with decreased rates of survival (OR, 2.14; 95% CI, 1.08–4.26). No underlying disease was predictive of mortality in the multivariate analysis.

DISCUSSION

This retrospective study revealed a statistically significant decrease in both overall and attributable mortality rates among patients with bacteremia who were receiving statins. A multivariate analysis confirmed that the reduced mortality rates were associated with statin therapy and were not simply an artifact of the retrospective analysis. This effect could not be related to the specific statin being given, because the number of patients receiving each of the different statins was small. In addition, the specific microbial etiology was not responsible for any of the observed differences in mortality.

The multivariate analysis revealed that ACE inhibitor use was associated with decreased rates of survival; however, there were no differences in the frequency of ACE inhibitor use between the patients who did and those who did not receive statins. The effect of ACE inhibitors may be related to the use of these drugs to treat patients with congestive heart failure, which is a condition associated with a higher mortality rate in a univariate analysis of all patients.

The severity of underlying illness often accounts for differences in survival among patients with bacteremia. In our study, there were few differences in the frequency of underlying diseases. Diabetes mellitus, hypertension, and coronary artery dis-

Table 4. Effect of statins on mortality in hospitalized patients with bacteremia.

Parameter	n/N (%) of patients		P[a]
	Who received statins	Who did not receive statins	
Overall hospital mortality	2/35 (6)	100/353 (28)	.002
Overall attributable mortality	1/35 (3)	70/353 (20)	.010
Staphylococcus aureus bacteremia	0/15 (0)	22/130 (17)	.128
Gram-negative bacteremia	1/19 (5)	48/223 (22)	.134
Community-acquired bacteremia	1/15 (7)	30/206 (15)	.489
Hospital-acquired bacteremia	0/20 (0)	40/147 (27)	.004

[a] Analyzed with 2-tailed Fisher's exact test.

Table 5. Microbial etiology of bacteremia and related attributable deaths among hospitalized patients taking statins and those not taking statins.

Type of bacteremia, organism	Patients who received statins (n = 35)		Patients who did not receive statins (n = 353)	
	No.	No. of deaths	No.	No. of deaths
Staphylococcus aureus bacteremia[a]				
Methicillin-susceptible *S. aureus*	10		94	13
Methicillin-resistant *S. aureus*	5		36	9
Gram-negative bacteremia[b]				
Escherichia coli	4		76	14
Klebsiella species	2		36	8
Pseudomonas species	2		30	10
Enterobacter species	4	1	16	3
Proteus species	2		16	3
Serratia species	4		3	
Acinetobacter species	0		7	2
Citrobacter species	0		6	1
Providencia species	0		5	1
Haemophilus influenzae	0		3	1
Campylobacter jejuni	0		2	1
Salmonella species	0		2	1
Morganella species	0		1	
Alcaligenes xylosoxidans	0		1	
Helicobacter pylori	0		1	
Yersinia enterocolitica	0		1	1
Bordetella avium	0		1	1
Mixed	2		16	3

[a] Total no. of cases, 145.
[b] Total no. of cases, 243.

ease were, as expected, more frequently encountered among those patients who were receiving statins. The only other underlying condition that was significantly different between the 2 groups was polysubstance abuse, which was more common among the patients who did not receive statins. Exclusion of these patients from data analyses did not alter the significance of the study in either overall or attributable mortality rates, nor did any underlying condition affect the observed differences in mortality rates in the multivariate analysis.

Although patients with hospital-acquired bacteremia and ICU stay had a higher mortality rate, this increased mortality rate was not evident among patients taking statins. Whereas adherence to medications before admission would be difficult to assess, patients with hospital-acquired infection would have been receiving medication under supervision.

Patients with bacteremia experience systemic inflammation and widespread proinflammatory cytokine release, which contribute to mortality. The beneficial effects of statins for patients with bacteremia may be related to their effects on the inflammatory process. The mechanism whereby statins may exert their anti-inflammatory effect involves depletion of isoprenoids, which are important nonsterol cholesterol precursors [9]. Isoprenoids are required for prenylation reactions in which farnesyl and geranyl groups are covalently bound to membrane G proteins, which are critical in the signal-transduction pathways and which regulate cellular signaling, migration, and proliferation [10–13]. By reducing the level of isoprenoids, statins inhibit the prenylation reaction and reduce cellular activity.

An important component of the inflammatory response is the chemotactic migration of neutrophils. Statins inhibit chemotaxis and transendothelial migration of neutrophils. Dunzendorfer et al. [14] treated neutrophils in vitro with pravastatin at therapeutically achievable concentrations and demonstrated a significantly reduced chemotaxis to the chemoattractant formyl-methionyl-leucyl-phenylalanine; this effect was not associated with a decrease in cholesterol levels. In a similar manner, statins have been shown to inhibit the migration of inflammatory cells and may thus decrease the inflammatory component of the atherosclerotic plaque [15].

Clinically, defects in neutrophil chemotactic activity are often associated with an increased incidence of skin and soft tissue infections. It is interesting to note that there was a statistically significant increase in skin and soft tissue infections among the patients with bacteremia who were receiving statins compared with those who did not receive statins. However, this finding may also be related to the increased incidence of diabetes mellitus in the statin group. Further study is necessary to delineate the potential permissive effect of statins in skin infection. The complete absence of pulmonary disease as a cause of bacteremic infection among the patients who received statin is unexplained.

The potential role of statins in the treatment of infections and other inflammatory states remains to be defined. Nevertheless, the results of this retrospective review suggest that prospective studies may demonstrate a therapeutic benefit and provide greater insight into the mechanisms involved in the inflammatory response.

Acknowledgments

We thank David M. Parenti, for careful review of the manuscript, the VAMC infection control nursing staff, and Howard Gale and Rebecca Shinol, for assistance in data collection.

References

1. Goldstein JL, Brown MS. Regulation of the mevalonate pathway. Nature **1990**; 343:425–30.

2. Byington RP, Jukema JW, Salonen JT, et al. Reduction in cardiovascular events during pravastatin therapy: pooled analysis of clinical events of the Pravastatin Atherosclerosis Intervention Program. Circulation **1995**; 92:2419–25.
3. Arntz HR. Evidence for the benefit of early intervention with pravastatin for secondary prevention of cardiovascular events. Atherosclerosis **1999**; 147(Suppl 1):S17–21.
4. Koenig W. Heart disease and the inflammatory response. BMJ **2000**; 321:187–8.
5. Sullivan GW, Sarembock IJ, Linden J. The role of inflammation in vascular diseases. J Leukoc Biol **2000**; 67:591–602.
6. Koh KK. Effects of statins on vascular wall: vasomotor function, inflammation, and plaque stability. Cardiovasc Res **2000**; 47:648–57.
7. Bellosta S, Bernini F, Ferri N, et al. Direct vascular effects of HMG-CoA reductase inhibitors. Atherosclerosis **1998**; 137(Suppl):S101–9.
8. Winn RK, Liu L, Harlan JM. Leukocyte adhesion and trafficking in acute inflammation [abstract 109.G]. In: Program and abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco). Washington DC: American Society for Microbiology, **1998**:764.
9. Casey PJ. Mechanisms of protein prenylation and role in G protein function. Biochem Soc Trans **1995**; 23:161–6.
10. Marshall CJ. Protein prenylation: a mediator of protein-protein interactions. Science **1993**; 259:1865–6.
11. Clapham DE. The G-protein nanomachine. Nature **1996**; 379:297–9.
12. Sinesky M. Recent advances in the study of prenylated proteins. Biochim Biophys Acta **2000**; 1484:93–106.
13. Casey PJ. Protein lipidation in cell signaling. Science **1995**; 268:221–5.
14. Dunzendorfer S, Rothbucher D, Schratzberger P, et al. Mevalonate-dependent inhibition of transendothelial migration and chemotaxis of human peripheral blood neutrophils by pravastatin. Circ Res **1997**; 81: 963–9.
15. Kreuzer J, Bader J, Janh L, et al. Chemotaxis of the monocytic cell line U937: dependence on cholesterol and early mevalonate pathway products. Atherosclerosis **1991**; 90:203–9.