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Early Statin Use is Associated with Increased Risk of Infection after Stroke

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Abstract

Infection after stroke is common and likely detrimental. Given the potent immunomodulatory properties of statins, we hypothesized that early statin use might increase the risk of infection in the immediate post-stroke period. In a study cohort of 112 patients with ischemic stroke, we found that early statin use was associated with increased risk of post-stroke infection. After controlling for stroke severity and patient age, the odds ratio (OR) and 95% confidence interval (CI) for infection in the first 15 days after stroke among patients on a statin by day 3 after stroke was 7.21 (1.40–37.98; $P=0.018$). When controlling for univariate predictors of infection, the OR associated for infection associated with statin use actually increased, but was no longer significant (8.49 [0.92–77.98]; $P=0.059$). Further, early statin use was associated with an increase in plasma interleukin-1 receptor antagonist (IL-1ra) which was significantly higher in early statin users than in non-statin users by day 7 after stroke. Our data suggest that early statin use appears to be associated with increased risk of post-stroke infection. This risk may, in part, be related to increases in plasma IL-1ra. If these findings are replicated in larger studies, they could have important implications for the timing of statin therapy after stroke.

Keywords

statins; stroke; infection; IL-1ra

Infection is common following stroke and associated with increased morbidity and mortality.^{1–3} Stroke severity appears to be the most important predictor of infection risk.^{1, 4–6} Recent experimental data suggest that ischemic brain injury may lead to a

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Disclosures

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“systemic immunodepression” that predisposes to infection.⁷ The degree of immunodepression appears to be related to stroke severity.^{8, 9}

Current guidelines recommend the use of statins to prevent recurrent ischemic stroke.¹⁰ The studies that established the benefits of statins in stroke prevention, however, did not enroll patients with severe stroke or patients in the immediate post-stroke period.^{11, 12} Current practice, however, is often to start statins during the initial hospitalization, while some even advocate immediate institution of statin therapy.^{13, 14} Given the potent immunomodulatory properties of statins, we hypothesized that these medications might further contribute to the risk of post-stroke infection. This study was a prospectively defined analysis of patients enrolled within 3 days of stroke onset who were followed longitudinally to assess immunologic outcomes. The original description of this cohort has been published.⁶

Patients and Methods

Patients

We enrolled patients with ischemic stroke admitted to Harborview Medical Center from 9/2005 through 5/2009 who were at least 18 years of age, could be enrolled within 72 hours of symptom onset and were felt not likely to die from their stroke. Patients with ongoing therapy for malignancy, known history of HIV, Hepatitis B or C, history of brain tumor, anemia (hematocrit < 35 on admission), and those taking immunosuppressive medications were excluded. The study was approved by the Institutional Review Board (IRB), and all patients or their surrogates provided informed consent.

Demographic and clinical data were collected on all patients. Stroke severity was determined by the National Institutes of Health Stroke Scale (NIHSS) score. Information about medications at the time of admission and hospital treatments for stroke were collected. MRIs were generally done within 24 hours of admission; infarct volume calculated from the diffusion weighted image by the ABC/2 method.¹⁵ Data regarding infections were actively tracked throughout the hospital course and defined as clinical symptoms of an infection (fever and/or pyuria for urinary tract infection [UTI] and fever and/or productive cough and radiographic evidence of consolidation for pneumonia [PNA]) and positive culture data (for both PNA and UTI). The analyses in this manuscript reflect the infections that occurred within 15 days after stroke onset. Of note, the acute stroke protocol in our hospital requires that patients remain NPO until they pass a swallow screen and that the use of bladder catheters be avoided.

Laboratory Studies

Blood was drawn on days 1, 3 and 7 after stroke onset. Plasma was immediately frozen at -80° ; the concentrations of circulating cytokines were later determined using a cytometric bead-based system (Fluorokine MAP®; R&D Systems). The cytokines assessed (and the lower limits of detection) for each are as follows: IL-6 (1.11 pg/mL), TNF- α (1.50 pg/mL), IL-2 (2.23 pg/mL), IL-1ra (10.91 pg/mL), and IL-10 (0.30 pg/mL). Values below the limit of detection are referred to as not detected (nd) and assigned the lowest limit of detection for statistical testing. Lipid status was assessed as soon as possible, and in all cases by 3 days, after stroke onset using standard methodology in the clinical laboratory.

Statistics

Descriptive data are presented as median and interquartile range (IQR) for continuous variables and percents for categorical variables. Group comparisons were performed using the Kruskal-Wallis test or the χ^2 test statistic as appropriate. Logistic regression was used to estimate odds ratio (OR) and 95% confidence interval (CI) for univariate associations of

clinical and demographic variables with the risk of infection in the first 15 days after stroke onset. Logistic regression was also used to test the association between statin use and infection within the first 15 days after stroke onset, both unadjusted and adjusted for important demographic and clinical variables with $P < 0.100$ in the univariate analyses. Patients started on statins later than 3 days after stroke onset or not at all were used as the reference group. Significance was set at $P = 0.05$ (two-tailed). Analyses were not adjusted for multiple comparisons.

Results

114 patients with acute ischemic stroke were enrolled in the study. One had ongoing infection (cellulitis) at the time of stroke onset and another died within the first week of the study; these 2 patients are excluded from further analyses. The median age of the remaining 112 patients was 57 (44–67) years, the median NIHSS score was 11 (4–19) and 65% were male. By day 15 there were 30 infections (9 pneumonias, 14 urinary tract infections and 7 others) in 28 patients. The data regarding these patients and their infections is detailed in the original publication from this study.⁶ At the time of admission (*ie.* stroke onset), 36 (32%) patients were on statins. Another 43 (38%) patients were started on statins within the first 3 days after stroke onset. The remaining 33 (29%) of patients were either started on statins at a later point in time or not at all. Table 1 depicts the differences between those patients on statins at the time of stroke (PTA), those started on statins early after stroke onset (early statin), and those who were either started on statins at a later time point or not at all (no statin). As might be expected, patients treated with statins tended to be older, and have more hypertension (HTN), coronary heart disease (CHD) and diabetes (DM) than those not on statins. Further, patients started on statins early after stroke onset had higher total cholesterol and low density lipoprotein (LDL) concentrations than those not started on statins. Of the patients started on a statin by day 3 after stroke, the most commonly prescribed drugs were atorvastatin (46%), simvastatin (30%) and pravastatin (14%). Most patients (63%) were prescribed a dose of at least 40 mg/day.

Univariate associations between infection risk by day 15 and these demographic and laboratory variable are shown in Table 2. Of these variables, stroke severity was the most potent predictor of infection, as measured by either NIHSS score or infarct volume. Infarct volume was also predictive of infection, but not as robustly as the clinical stroke severity. A history of CHD and higher plasma high density lipoprotein (HDL) were also associated with increased risk of infection. In fact, HDL was 45 mg/dL (30, 52) at day 3 among those who became infected and 35 mg/dL (28, 43) in those that did not ($P = 0.031$).

Table 3 depicts the association between statin use and infection risk, both unadjusted and adjusted for the important variables described in Table 2. Since stroke severity and infarct volume are highly correlated (Spearman Rank Order $r = 0.750$; $P < 0.001$), we controlled only for stroke severity in the multivariate model. After controlling for stroke severity and patient age, statin exposure prior to or within 3 days of stroke onset was associated with at least a fourfold increase in the risk of infection. Among patients on statins PTA, the drugs were stopped in 8 at the time of hospital presentation. If these patients are excluded from the analyses, the risk of infection associated with early statin use was even higher. Further, the risk of infection related to statin use actually increases after controlling for the variables defined univariate analyses (CHD and baseline HDL), but the associations are no longer significant. If only statin naïve patients are included in the analyses ($N = 76$), the power to show an association between statin use and infection decreases, but the general findings are essentially unchanged (Table 3, row 4). Given the small numbers of patients we were unable to detect a difference in infection risk based on the particular statin used or the dose prescribed.

Given the well described immunomodulatory effects of statins, concentrations of both pro-inflammatory and immunomodulatory cytokines were assessed at days 3 and 7 after stroke onset (Table 4). There were no differences in cytokine concentrations among statin users and non-users at 3 days after stroke onset, but by day 7 after stroke, patients on statins at this time point had significantly higher concentrations of IL-1ra than those not on statins. If the analyses in Table 3 are controlled for either initial IL-1ra or day 7 IL-1ra concentrations, the effect of statins on infection risk is lost.

Discussion

In this study we identified an association between early statin use and the risk of post-stroke infection; the odds ratio for infection in the first 15 days after stroke was at least 4 times higher in patients on statins at stroke onset or started on statins within the first 3 days after stroke onset in comparison to those started on statins at a later time point or not at all. That statins could affect the risk of infection is suggested by their potent immunomodulatory properties.¹⁶ The post-stroke period represents a time when the risk of infection is known to be especially high. This increased risk of infection is related to stroke severity and appears to be caused by a sympathetically mediated depression in immune cell function.⁷ It is thus plausible that administration of immunomodulatory agents like statins could further increase the risk of infection. In fact, a small randomized trial of simvastatin *versus* placebo for treatment of acute (within 12 hours) ischemic stroke showed that patients allocated to simvastatin were more than twice as likely (OR 2.4, 1.06–5.4) to develop infection than those allocated to placebo.¹⁷

There are multiple potential mechanisms by which statins might increase the risk of infection. Statin can interfere with initiation of the innate immune response.¹⁸ They are known to decrease the expression of the major histocompatibility molecule (MHC) II and inhibit T_H1 mediated immune responses.¹⁶ Further, they are known to inhibit the secretion of pro-inflammatory cytokines.^{19–21} We did not observe any differences in the concentration of pro-inflammatory cytokines like TNF- α or IL-2 related to statin use. At 3 days after stroke onset, patients who were on statins PTA had higher concentrations of IL-6, a cytokine that is often considered a general marker of inflammation.²² By day 7 after stroke onset this difference was no longer significant. IL-10 is an immunomodulatory cytokine infection linked to post-stroke infection.²³ In our patient cohort, we observed neither a link between IL-10 and infection risk nor IL-10 and statin use.⁶ In a recent publication based on the same patient population as the current study, we found that elevated plasma IL-1ra was independently associated with the risk of post-stroke infection.⁶ Most studies tend to address the effect of statins on production of T_H1 and T_H2 type cytokines, few have addressed the effect of statins on production of immunosuppressive cytokines like IL-1ra. In one study, however, statins were shown to enhance IL-1ra secretion from lipopolysaccharide (LPS) stimulated whole blood obtained from patients with hypercholesterolemia.²⁴ Given that the association between statin use and infection risk is abrogated after controlling for plasma IL-1ra in this study, it suggests that statin induced increases in IL-1ra may be important in mediating the increased risk of infection.

Retrospective and observational studies suggest statins might be neuroprotective in that patients on statins have been reported to have smaller infarcts and better outcomes than patients not on statins at the time of stroke.^{14, 25} In our relatively small study, we saw no effect of statin use on stroke severity or infarct size (Table 1). The confounding issue is that the mechanism of infarction in patients treated with statins prior to stroke onset likely differs from the mechanism of stroke in non-statin treated patients, as suggested by the greater frequency of HTN, CHD, and DM in patients exposed to statins at the time of stroke onset.

Whether or not statins have neuroprotective properties will need to be addressed in an appropriately powered prospective randomized controlled trial.

There are also data that suggest discontinuation of statin therapy can precipitate ischemic events.^{26–28} If statins really do increase the risk of post-stroke infection, the absolute risk of statin discontinuation would need to be weighed against this risk of infection given that post-stroke infection is independently associated with worse outcome.^{1–3} We had too few patients in whom statins were stopped after admission to address potential problems associated with statin withdrawal. Given the immunomodulatory properties of statins, their potential use in patients with infection and sepsis has been evaluated. While many of these studies suggest a benefit to statin use, others do not.²⁹ Another recent study randomized statin users with infection to statin continuation or discontinuation at hospital admission and found no benefit to continued statin use or harm to statin discontinuation.³⁰ Importantly, these studies address the treatment of infection related inflammation by statins and not the risk of developing infection. It is clear that infection risk is high in the immediate post-stroke period due to systemic immunodepression, and statin induced immunomodulation may further increase this risk of infection.

Limitations of this study are the small size and its observational nature. Nonetheless, there is the suggestion of an effect of statin use on infection risk; in individuals not previously on statins, controlling for important predictors of infection, such as stroke severity, only increased the apparent risk of statin use. Statin users were more likely to have DM, HTN and a history of CHD, suggesting that the drugs were prescribed to patients with worse overall health. Only CHD, however, was independently associated with infection risk in this study. Relative strengths of the study include the diverse patient population and active surveillance for infections.

In summary, most studies demonstrate that stroke severity is by far the most important predictor of infection risk following stroke, and this risk may be mediated by systemic changes in the immune response that predispose to infection. The current study also suggests that early statin use may independently confer an increased risk of post-stroke infection. And while the data to support a role for high dose statins in secondary stroke prevention are convincing, these prevention studies excluded patients with severe strokes and, importantly, did not enroll patients in the immediate post-stroke period.^{31, 32} The potential that statins contribute to post-stroke infection needs to be confirmed in larger patient cohorts, as it could have important implications for the timing of statin therapy after ischemic stroke. If the results in this small study are confirmed, it would be reasonable to delay the administration of statins until after the immediate post-stroke period to avoid the possible risk of increased infection given that their effect on secondary prevention is one that plays out over several years of follow up.^{31, 32}

Acknowledgments

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Table 1

Differences between patients on statins at admission (statin PTA), those not on a statin at admission but started on a statin by day 3 and those patients started on statins at a later time point or not at all (no statin). Statistics are by Kruskal-Wallis H test or by χ^2 as appropriate.

	statin PTA N=36	statin by day 3 N=43	no statin N=33	P
age (years)	66 (54–70)	58 (48–67)	42 (34–50)	<0.001
female	12 (33%)	11/43 (26%)	16/33 (48%)	0.113
NIHSS score	12 (4–22)	8 (4–18)	12 (3–18)	NS
infarct volume (mL)	10 (2–117)	11 (1–51)	33 (1–131)	NS
medical history				
AF	5/36 (14%)	4 (9%)	7/33 (21%)	NS
HTN	30/36 (83%)	20/43 (46%)	9/33 (27%)	<0.001
CHD	19/36 (53%)	5/43 (12%)	1/33 (3%)	<0.001
DM	19/36 (53%)	7/43 (16%)	1/33 (3%)	<0.001
tobacco use	12/36 (33%)	16/43 (37%)	15/33 (45%)	NS
lipids at presentation				
total cholesterol (mg/dL)	168 (135–198)	187 (166–211)	146 (134–188)	0.004
LDL (mg/dL)	95 (81–117)	123 (97–148)	86 (70–114)	<0.001
HDL (mg/dL)	35 (26–44)	41 (32–50)	35 (28–45)	0.112
infection by day 15	14/36 (36%)	11/43 (26%)	4/33 (12%)	0.071

PTA=prior to admission, NIHSS=National Institutes of Health Stroke Scale, AF=atrial fibrillation, HTN=hypertension, CHD=coronary heart disease, DM=diabetes mellitus, LDL=low density lipoprotein, HDL=high density lipoprotein. NS=P 0.20.

Table 2

Univariate predictors of infection to day 15.

	OR (95% CI)	P
NIHSS score (per point)	1.16 (1.09, 1.23)	<0.001
infarct volume (per 10 cc)	1.08 (1.04, 1.13)	<0.001
age (per year)	1.02 (0.99, 1.05)	NS
gender (female)	1.05 (0.43, 2.58)	NS
medical history		
AF	0.91 (0.39, 2.15)	NS
HTN	1.05 (0.44, 2.47)	NS
CHD	4.10 (1.58, 10.63)	0.004
DM	1.74 (0.67, 4.49)	NS
tobacco use	1.30 (0.54, 3.11)	NS
lipids at presentation		
total cholesterol (per 10 mg/dL)	1.06 (0.94, 1.19)	NS
LDL (per 10 mg/dL)	1.02 (0.89, 1.16)	NS
HDL (per 10 mg/dL)	1.31 (0.99, 1.74)	0.063

NIHSS=National Institutes of Health Stroke Scale, AF=atrial fibrillation, HTN=hypertension, CHD=coronary heart disease, DM=diabetes mellitus, LDL=low density lipoprotein, HDL=high density lipoprotein. NS= $P \geq 0.20$.

Table 3

Effect of statin exposure on infection risk by day 15 after stroke.

model adjusted for:	unadjusted		NIHSS score, age		NIHSS score, age, CHD history, admission HDL	
	OR	P	OR	P	OR	P
patient on statin PTA or statin started by day 3 (patients on a statin PTA, irrespective of whether it was continued or stopped at admission, are included in the statin group)	3.16 (1.00, 9.99)	0.050	5.63 (1.23, 25.75)	0.026	5.37 (0.81, 35.37)	0.081
patient not on statin PTA and statin continued, or statin started by day 3 (patients on a statin PTA but in whom the statin was stopped at admission are included in no-statin group)	2.25 (0.86, 5.87)	0.097	3.93 (1.14, 13.50)	0.030	4.37 (0.95, 20.22)	0.059
patient on statin PTA and statin continued, or statin started by day 3 (patients on a statin PTA but in whom the statin was stopped at admission are excluded from analysis)	3.17 (0.99, 10.16)	0.052	7.21 (1.40, 37.98)	0.018	8.49 (0.92, 77.98)	0.059
patient not on statin PTA but started by day 3 (non-statin group includes only those patients not on a statin PTA and not started on a statin by day 3)	2.49 (0.714, 8.697)	0.152	4.62 (0.76, 28.09)	0.097	7.57 (0.77, 64.62)	0.083

PTA = prior to admission, OR = odds ratio, CI=confidence interval, NIHSS = National Institutes of Health Stroke Scale, CHD = coronary heart disease, HDL = high density lipoprotein

Table 4

Differences in plasma cytokines at 3 days and 7 days after stroke onset based on statin use at each time point. Statistics are by Mann-Whitney U test.

		statin use	no statin use	P
day 3	IL-6 (pg/mL)	2.06 (nd, 11.09) N=60	1.52 (nd, 4.60) N=38	NS
	TNF α (pg/mL)	1.71 (nd, 3.09) N=59	1.86 (nd, 2.84) N=38	NS
	IL-2 (pg/mL)	nd (nd, nd) N=59	nd (nd, nd) N=37	NS
	IL-1ra (pg/mL)	1659 (1088, 3057) N=58	1685 (919, 3652) N=36	NS
	IL-10 (pg/mL)	nd (nd, 0.81) N=59	nd (nd, 0.60) N=38	NS
day 7	IL-6 (pg/mL)	1.61 (nd, 5.35) N=71	nd (nd, 2.57) N=23	NS
	TNF α (pg/mL)	2.04 (nd, 3.69) N=72	2.12 (nd, 4.16) N=23	NS
	IL-2 (pg/mL)	nd (nd, nd) N=72	nd (nd, nd) N=23	NS
	IL-1ra (pg/mL)	2054 (1306, 3732) N=72	1169 (903, 2340) N=23	0.017
	IL-10 (pg/mL)	nd (nd, 0.71) N=72	nd (nd, 1.08) N=23	NS

IL=interleukin, TNF=tumor necrosis factor, IL-1ra=IL-1 receptor antagonist, nd=not detected, NS= $P > 0.20$.