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Does Statin Usage Reduce the Risk of Corticosteroid-related Osteonecrosis in Renal Transplant Population?

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Abstract

The relationship between corticosteroids and osteonecrosis is well known. Limited data suggest that statins modulate cholesterol metabolism and may protect against osteonecrosis. We analyzed our prospective renal transplant database to determine if statin usage reduces the incidence of corticosteroid-related osteonecrosis. We identified 2,881 renal transplantation patients who met our entry criteria. Among 338 patients on statins, 15 (4.4%) developed osteonecrosis versus 180 of 2543 (7%) patients who were not on statins. Osteonecrosis-free survival was similar in patients with and without statin exposure.

Introduction

Osteonecrosis (ON) is a disabling disease and its pathogenesis is associated with corticosteroid exposure, ethanol usage, coagulapathies, and lupus erythematosus. It is an important orthopaedic complication of corticosteroid immunosuppression after solid organ transplantation occurring with a frequency of 3 to 41%.[1-3] Abnormalities of lipid metabolism, fat overload, and intraosseous hypertension have been cited frequently as important in the development of ON.[4-6] Previous studies suggest that ON develops in 5 to 11% of organ transplant patients within 1 year after the transplant, [7-9] but it is not possible to predict which patients receiving corticosteroids will develop ON. Aside from minimizing the exposure to corticosteroids or other risk factors, there are no definite measures available to prevent ON.[10-12]

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Animal and limited clinical data have suggested that statins may have a protective role against ON. Wang and other authors [13-18] have shown that corticosteroids cause the marrow pluripotent cells to differentiate into fat cells through down-regulation of Cbfa1/Runx2 gene expression and osteocalcin promoter activity while increasing the expression of adipose-specific genes 422(aP2) and PPARγ2. Statins do the opposite, by decreasing adipogenic and stimulating osteogenic differentiation through suppressing PPARγ2 and increasing Cbfa1/Runx2 expression in bone marrow mesenchymal cells.

Our goal was to determine if statin usage, in renal transplantation patients, is associated with a reduction in incidence of osteonecrosis.

Materials and Methods

Study design

Our transplant recipient data is prospectively gathered and maintained in a computer data base with the funding provided by the National Institutes of Health (NIH, Bethesda, MD). Using this database [19,20] we retrospectively identified 3399 patients who had a renal transplant between January 1985 and December 2003. This time period was selected to allow a minimum follow-up of 3 years after the transplantation. Entry criteria were patients greater than or equal to 16 years of age, first-time renal transplants, and no prior corticosteroid exposure. Statin usage was defined as being on a statin drug at the time of transplant or initiated within 31 days after transplant and continuing for at least 1 year duration. This time period was selected based upon the finding that ON commonly develops within the first year after transplantation. [7-9] The indication for statin treatment was hypercholesterolemia. Dosages were adjusted by the treating physician until the cholesterol level was reduced to the clinically appropriate target range. The most commonly used statin drugs were Advicor® (niacin 500 mg + lovastatin 20 mg; Kos Pharmaceuticals, Inc, Cranbury, NJ), atorvastatin (Lipitor®, Pfizer Inc, New York, NY), crivastatin (Baycol®, Bayer AG, Leverkusen, Germany), rosuvastatin (Crestor®, AstraZeneca PLC, London, UK), fluvastatin (Lescol®, Novartis AG, Basel, Switzerland), lovastatin (Mevacor®, Merck and Co, Inc, Whitehouse Station, NY), pravastatin (Pravachol®, Bristol-Myers Squibb Co, New York, NY), and simvastatin (Zocor®, Merck and Co, Inc).

Power analysis

We performed a power analysis to determine what potential difference in ON-free survivorship we would have been able to detect, given the size of our patient cohort, at five and ten years after transplantation. At power = 95% and level of significance $p = 0.05$, our data were sufficient to detect a difference in ON-free survival, if it was present, of 3% at 5 years (statin exposure group 91% versus non-statin exposure group 94%) and 5% at 10 years (statin exposure group 88% versus non-statin exposure group 93%).

Demographics

There were 2881 patients who met the entry criteria. There were 1752 (61%) male and 1129 (39%) female patients. Among the 2881 patients, 1619 had varying levels of exposure to statins; however, only 338 patients met our on-statins definition.

There were 338 (12%) patients in the statin cohort and 2543 (88%) in the non-statin cohort (Table 1). In the statin cohort, 180 (53%) were males and 158 (47%) were females. In the non-statin cohort 1572 (62%) were males and 971 (38%) were females. The mean age of the overall patient cohort was 43 years (range, 16–77 years) and mean follow-up was 128 months (range, 36–242 months). In the statin cohort, mean age was 47 years (range 23-74) and mean follow-up 91 months (range 43-229) and in the non-statin cohort the mean age was 42 years (range

16-247) and mean follow-up 136 months (range 43-247). The most common primary diagnosis that led to end stage renal failure was diabetic nephropathy. Patients were prospectively followed by regular clinic visits. We depended upon self-reporting of fractures, ON, joint pain, or arthritis (not otherwise specified) as noted in the charts. The medical record was reviewed for any patients reporting joint pain (not otherwise specified) to verify the diagnosis and look for other possible etiologies. Data gathered consisted of name, gender, age, indication and transplant type (living twin, living non-twin, cadaver), transplant date, preemptive transplant (transplant without prior dialysis), post-dialysis transplant, number of rejection episodes, statin drug usage (yes/no), No patients were contacted specifically for this study and only chart data was reviewed.

Statistical analysis

Multivariate Cox regression tests [21] were used to analyze ON-free survival on statins and other variables including gender, rejection episodes, and year of transplantation. Survivorship analysis was performed using Kaplan-Meier methods with the endpoint defined as occurrence of ON. [22] Log-rank and Wilcoxon tests were performed for comparison of data between the statins vs. non statin cohort to determine whether there was a relationship between the time course for development of ON and statin usage. The data were analyzed using SAS for Windows statistical software package (Version 9.1 2003; SAS Institute Inc, Cary, NC).

Results

In the overall patient cohort of 2881 patients, 195 (7%) developed ON in 286 joints. In the femoral head, 96 patients developed ON unilaterally and 91 bilaterally. Eight patients had involvement of other bones. Among the 338 patients in the statin cohort, 15 patients (4.4%) developed ON at 23 sites (all involving the femoral head). In the non-statin cohort of 2543 patients, 180 patients (7%) developed ON at 263 sites (255 femoral heads and eight other sites). ON-free survival stratified by statin usage did not show a relationship between statin exposure and development of ON ($p = 0.14$, log-rank) (Fig 1). At 5 years, the ON-free survivorship for those patients on statins versus not on statins was 96% ± 2.1% (95% confidence interval) versus 94% ± 1.0% (95% C.I.). Cox regression revealed that statin usage did not predict ($p = 0.8$) ON-free survival. Other variables (Table 2) that were associated with a higher incidence of ON were (1) male gender ($p = 0.008$), (2) higher number of rejection episodes ($p = 0.009$), and (3) earlier year of transplant ($p = 0.01$).

Discussion

Osteonecrosis is an important orthopaedic complication of corticosteroid immunosuppression after solid organ transplantation with poorly understood pathogenesis. Aside from minimizing the exposure to corticosteroids or other risk factors, there are no definite measures available to prevent ON. Our goal was to determine if statin usage, in renal transplantation patients, is associated with a reduction in incidence of osteonecrosis.

Prior reports suggest a relationship between statins and ON. Wang and co-authors [15,18] have shown corticosteroids cause the marrow pluripotent cells to differentiate into fat cells through down-regulation of Cbfa1/Runx2 gene expression and osteocalcin promoter activity while increasing the expression of adipose-specific genes 422(aP2) and PPARγ2. Statins do the opposite by decreasing adipogenic and stimulating osteogenic differentiation through suppressing PPARγ2 and increasing Cbfa1/Runx2 expression in bone marrow mesenchymal cells.[13,14,16,23] This may or may not be related to their known mechanism of action in lowering cholesterol via inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase. The effect of corticosteroids and statins is concentration and time dependent.[13-16,23-26] Corticosteroids are a clear risk factor for ON, and therefore, with these animal and laboratory

findings in mind, we investigated whether or not statins have a protective role against ON in humans.

Pritchett's study in 2001 [17] reported a protective role of statins against ON in humans. He reported the incidence of ON of 1% in 284 patients on statins, which appears less than the historical incidence of 5% to 11% previously reported in the literature. [7-9] He concluded statins may protect against the development of ON in patients receiving corticosteroid treatment. However, his study was retrospective with poorly controlled entry criteria. There were no controls other than historical controls. In addition, the study group was a heterogeneous group of patients with respect to corticosteroid indication.

Our large patient cohort was powered sufficiently (significance level $p = 0.05$, 95% power) to detect a reduction in risk as small as 3% at 5 years and 5% at 10 years in the incidences of ON. We did not identify any risk reduction, therefore, given our definition of statin exposure, if a reduction in ON incidence exists it likely is less than 5% at 10 years. We believe a reduction of risk of 5% or less is of dubious clinical importance.

The number of rejection episodes, a surrogate of peak corticosteroid exposure, was associated with the development of ON. This would be expected given the body of knowledge identifying a relationship between corticosteroids and ON. As all our patients were on corticosteroid immunosuppression, we could not study if actual corticosteroid exposure was related to ON development. However, our data demonstrated that a higher number of rejection episodes was associated with a higher incidence of ON.

Our data also suggest that male gender is associated with an increased risk (34%) of ON compared to females. To our knowledge, this has not been reported previously. The explanation for this finding is unknown yet a gender difference related to differing fat metabolism may be a factor.[27,28]

Our study has some limitations. The methodology is suboptimal because it is not a randomized prospective study, however, the large size of the patient cohort and the statistical significance achieved support the validity of the results and conclusion. Some of the patients assigned to the non-statin group actually had some limited exposure to statins, but not enough to meet the specific defined criteria for this study. The definition for statin usage was delineated to identify those patients who were taking statins at the time of highest risk for developing osteonecrosis. Therefore, although the non-statin group is not a pure non-statin group, its composition is justified biologically. Asymptomatic patients with ON were not captured as most of the cases were self-reported and prospective MRI screening was not done routinely. Although prevalence of asymptomatic ON has been reported between 6% to 9% in various studies [29-31] and the detection of asymptomatic disease is interesting, it is unlikely to change a patient's disease management. Fortunately, asymptomatic disease tends to have a benign course in majority of patients. [29,30] In some rare cases, spontaneous resolution has been documented. [32]

This study included only renal transplant patients so the data may or may not be applicable to patients at risk for ON for other reasons. While it would have been useful to analyze the relationship between cholesterol levels and ON we did not have sufficient data on cholesterol levels to perform such an analysis, however, dosages were modified in principle to reduce cholesterol to clinically appropriate levels. All statins may not be the same. Nevertheless, we are not aware of data to suggest that therapeutic dosages of different statins have a variable influence on the pathophysiology of ON. Finally, as all our patients were on corticosteroid immunosuppression, we could not study if actual corticosteroid exposure was related to ON development. We believe that the large size and homogeneity of our patient cohort, from a single transplant center, with the prospective collection of data, partially offset these

deficiencies. Despite the stated limitations of this study, the data and analysis provides important new information in our knowledge of ON and it is unlikely that a randomized, prospective study will be performed to address this study's goal.

We conclude that among renal transplant patients, statin usage does not appear to lower the risk of ON. Large scale, randomized trials might reveal a reduced incidence of ON related to statin usage but it is unlikely to be very large. The number of rejection episodes and male gender was associated with a higher risk.

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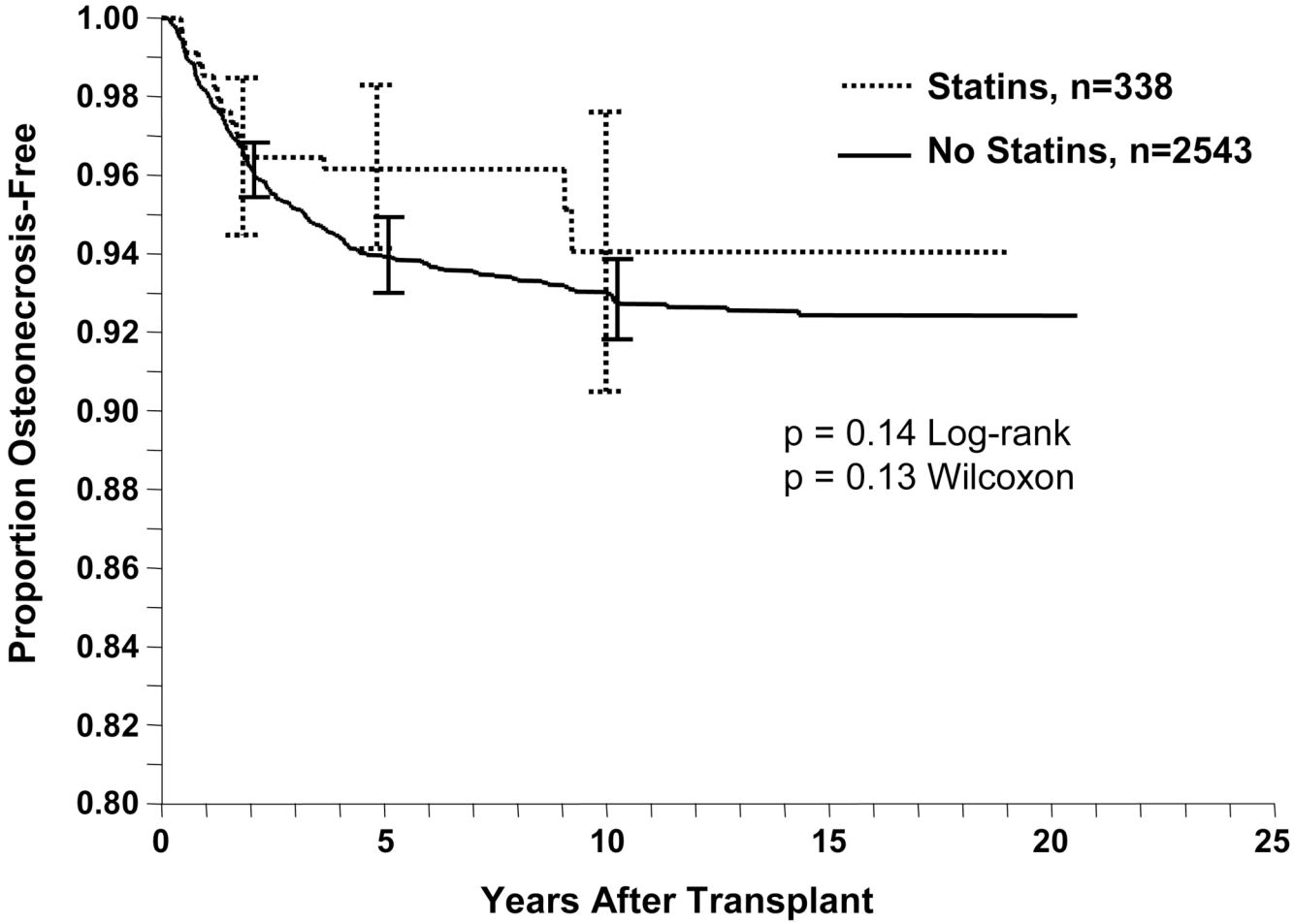

Fig 1.

A univariate Kaplan-Meier life table analysis of ON-free survival of kidney transplant patients on statins identified no trend in ON risk reduction for patients taking statins (p = 0.14, log-rank). Error bars = 95% confidence intervals.

TABLE 1

Demographics of Study Cohort

Variable	Value
Total number of patients	2881
Male: female	1752 (61%):1129 (39%)
Age (years)*	43 ± 12.8 (16–77)
Follow-up (months)*	128 ± 57.8 (36–242)
Statin usage: no statin usage	338/2881 (12%):2543/2881 (88%)
Total number of patients with osteonecrosis	195 (7%)
Total number of sites affected	286
Femoral head	278
Other	8

*Values are expressed as mean ± standard deviation, with range in parentheses

TABLE 2
Cox Multivariate Analysis Table of Predictors with Relative Risk

Predictor	Adjusted Relative Risk (95% Confidence Interval)	p Value
Gender (as male)	1.52 (1.11–2.09)	0.008
Number of rejection episodes	1.17 (1.04–1.32)	0.009
Year of transplant	0.96 (0.93–0.99)	0.01
Statin use	1.08 (0.61–1.91)	0.8