Association of the Use of Statins with Disease Activity and Functional Status in Puerto Ricans with Rheumatoid Arthritis

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Objective: Statins, which appear to have anti-inflammatory and immunomodulatory effects, may benefit patients with rheumatoid arthritis (RA). Our study sought to determine the association of statins use with disease activity and functional status in a group of patients with RA.

Methods: A cross-sectional study was performed in 209 Puerto Ricans with RA (per the 1987 classification criteria of the American College of Rheumatology). Demographic features, lifestyle-related behaviors, disease activity (per Disease Activity Score 28), comorbid conditions, functional status (per Health Assessment Questionnaire), pharmacologic therapy, and patients' and physicians' global assessments using visual analogue scales, were determined. Data were examined using univariate, bivariate, and multiple logistic regression analyses.

Results: The mean (standard deviation [SD]) age of the study population at study visit was 56.8 (13.5) years (range: 24-86 years); 175 patients (83.7%) were women. The mean (SD) disease duration was 10.4 (9.5) years (range: 0.0-44.0 years). Thirty-two (15.3%) patients were using statins at study visit, and 36 (17.2%) had used statins in the past. In the multivariable analysis, the current use of statins was associated with higher functional status (odds ratio 0.42, 95% confidence interval 0.22-0.80) than was nonuse, after adjusting for age, disease duration, arterial hypertension, coronary artery disease, and dyslipidemia. No association between either current or past use of statins and disease activity was found.

Conclusion: In this group of RA patients, the current use of statins was associated with a higher functional status; conversely, no association was found between statins use and disease activity. However, larger and longitudinal studies are required to confirm these findings. [*P R Health Sci J 2014;33:3-8*]

Key words: Rheumatoid arthritis, Statins, Disease activity, Functional status, Puerto Ricans

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint inflammation and destruction, which may negatively impact patient's functional capacity, quality of life, and working ability (1). The persistent state of inflammation which has been described in RA may promote the progression of atheromatous lesions, thus conferring an increased risk for developing coronary artery disease (CAD) (2). Indeed, RA has been identified as an independent risk factor for CAD (2), with CAD by itself being one of the main causes of morbidity and mortality in RA, particularly in patients with long-standing disease.

Hydroxyl-methyl-glutaryl coenzyme A (HMG-CoA) inhibitors (statins) are indicated for lowering cholesterol levels in patients with hyperlipidemia. However, the benefits of statins may not be limited to their cholesterol-lowering properties or to their impact on the prevention of CAD as recent studies have shown that statins possess anti-inflammatory and immunomodulatory properties (3). For instance, simvastatin suppresses the secretion of proinflammatory cytokines (4) and induces the apoptosis of fibroblast-like synoviocytes derived from RA patients (5). The immunomodulatory role of statins has been demonstrated by studies showing that atorvastatin increases the number of regulatory T cells and restores their suppressive function in

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RA patients (6). Furthermore, studies have shown that there is an association between statins therapy and the reduced risk of developing RA in patients with hyperlipidemia (7-8).

Although statins appear to have anti-inflammatory and immunomodulatory effects, the clinical benefits of this class of drugs in terms of disease activity and outcome in RA remain to be elucidated. Therefore, we examined a group of patients with RA to evaluate the impact of statins on disease activity and functional status.

Methods

Patient population

A cross-sectional study was performed in 209 patients with RA. All of the patients were ≥ 21 years old, had Puerto Rican ethnicity (self and 4 grandparents), and met the revised (1987) criteria of the American College of Rheumatology (ACR) classification for RA (9). Patients were evaluated from February 2007 to April 2008 at the rheumatology clinics of the University of Puerto Rico Medical Sciences Campus (UPR-MSC) in San Juan, Puerto Rico, as well as at 3 private rheumatology practices, also located in San Juan, Puerto Rico. The study was approved by the UPR-MSC Institutional Review Board.

RA patients had their routine visits at 2- to 3-month intervals. Additional visits were scheduled as needed (based on disease activity, complications, or both). At each routine visit, laboratory tests such as complete blood cell count, serum chemistries, urinalysis, erythrocyte sedimentation rate (ESR), and lipid panel were routinely ordered. At the time of the study visit, a structured clinical form was completed for each patient to gather data about demographic parameters, lifestyle behaviors, clinical manifestations, comorbidities, pharmacologic treatments, disease activity, and functional status. This form was developed by the UPR-MSC Rheumatology Division to evaluate clinical information uniformly and to allow the assessment of RA outcome measures at each patient's visit. When necessary, the medical records of RA patients were reviewed to gather further information about clinical manifestations, comorbidities, and pharmacologic therapies.

Variables

The following demographic features were examined: age, gender, and disease duration. Age at onset was defined as the age at which the patient had the first symptom attributable to RA, and age at diagnosis as the age at which the patient met the ACR criteria for RA. Disease duration was defined as the time interval between RA diagnosis and study visit. Lifestyle behaviors, including cigarette smoking, consuming alcohol, and exercising, were also evaluated. The latter was defined as regular participation in physical activity as part of a personal fitness plan. Cumulative RA manifestations and the presence of comorbid diseases were determined at study visit. RA manifestations examined included joint deformities/contractures (defined as loss of more than 20% of range of motion, lax collaterals, malalignment, or subluxation), radiographic evidence of joint damage, joint replacement surgeries, and extra-articular manifestations (subcutaneous nodules and ocular [keratoconjunctivitis sicca, episcleritis, scleritis, scleromalacia, or uveitis], pulmonary [pleuritis, pleural effusion, pulmonary nodules, interstitial lung disease, or pulmonary fibrosis], cardiac [pericarditis, myocarditis, valvular nodules, or coronary vasculitis], and neurologic [neuropathies, peripheral neuropathy, or mononeuritis multiplex] manifestations). The following comorbid conditions were determined: type 2 diabetes mellitus, arterial hypertension, dyslipidemia, coronary artery disease (angina, myocardial infarction, and/or coronary artery bypass graft), and metabolic syndrome (per the American Heart Association and National Heart, Lung, and Blood Institute classification) (10). Cumulative exposure to corticosteroids and traditional and biologic disease-modifying anti-rheumatic drugs (DMARDs) was examined. Also, the current (within the last month) and past uses (up to a month prior to the evaluation date) of statins were determined.

Disease activity was assessed using the European League Against Rheumatism (EULAR) Disease Activity Score 28 (DAS 28) (11). The DAS28 uses the 28-joint count, the ESR, and the patient's visual analogue scale (VAS) for overall health to assess disease activity. Functional status was assessed with the Health Assessment Questionnaire Disability Index (HAQ) (12). The HAQ is a 20-question validated instrument that assesses the degree of difficulty a patient has in accomplishing each of 8 functional tasks (dressing, rising, eating, walking, hygiene, reaching, gripping, and performing usual activities). HAQ scores range from 0 to 3, with higher scores representing greater levels of disability. The patient's global assessment and perception of pain were determined by visual analogue scales (13-14). In addition, the physician's global assessment, and functional impairment and physical damage assessments of the patients studied were also determined using visual analogue scales (13-14).

Statistical analysis

Descriptive analyses were performed using the mean, standard deviation (SD), median, and interquartile range (IQR) for continuous variables; frequencies and percentages were used for categorical variables. A comparison between current and past use of statins was made using the unpaired t-test (or the Mann–Whitney U test) and Pearson's chi-squared test (or Fisher's exact test), as appropriate. To study the association between disease activity and functional status and the current use of statins, contingency tables were constructed. Variables with a p value ≤ 0.10 in these analyses were entered into multivariable logistic regression models. The statistical software STATA version 11 (StataCorp, College Station, TX, USA) was used to performed the statistical analysis.

Results

A total of 209 patients with RA were examined; 175 of the patients (83.7%) were women. The mean age (standard deviation [SD]) of the study population at the time of the study visit was 56.8 (13.5) years (range: 24-86 years), and the mean (SD) disease duration was 10.4 (9.5) years (range: 0.0-44.0 years). Table 1 shows the demographic features, lifestyle behaviors, clinical manifestations, disease activity, comorbidities, and functional status of the study patients.

Table 1. Demographic features, lifestyle-related behaviors, clinical manifestations, disease activity, comorbidities, and functional status of rheumatoid arthritis (RA) patients (n = 209)

Features	
Age, mean years (SD)	56.8 (13.5)
Age at RA onset, mean years (SD)	44.8 (13.8)
Age at RA diagnosis, mean years (SD)	46.4 (14.1)
Disease duration, mean years (SD)	10.4 (9.5)
Gender, % female	83.7
Alcohol use, %	3.8
Smoking, %	9.1
Exercise, %	18.7
Joint deformities/contractures (n = 208), %	56.7
Joint surgeries (n = 208), %	18.3
Extra-articular manifestations	64.1
Erythrocyte sedimentation rate (n = 200), mean mm/hr (SD)	31.8 (23.6)
DAS28 (n = 206), mean score (SD)	3.6 (1.7)
Body mass index, mean kg/m2 (SD)	28.0 (6.0)
Type 2 diabetes mellitus, %	12.0
High blood pressure, %	55.5
Dyslipidemia, %	51.2
Metabolic syndrome (n = 207), %	39.6
Coronary artery disease (n = 207), %	6.3
Corticosteroid use, %	78.0
DMARDs use (n = 208), %	96.6
HAQ score (n = 204), mean score (SD)	1.1 (0.8)
Patient's global assessment (n = 208), mean mm (SD)	39.8 (32.4)
Patient's pain assessment (n = 208), mean mm (SD)	40.0 (32.2)
Physician's global assessment (n = 208), mean mm (SD)	19.6 (22.5)
Physician's functional impairment assessment (n = 208), mean mm (SD)	22.1 (23.7)
Physician's physical damage assessment (n = 208), mean mm (SD)	18.1 (23.0)

SD: Standard deviation; CABG: Coronary artery bypass grafting; DMARDs: Disease-modifying anti-rheumatic drugs; DAS28: Disease Activity Score 28; HAQ: Health Assessment Questionnaire

Current users of statins (n = 32) were compared to current nonusers of statins (n = 177), and past users of statins (n = 36) were compared to past nonusers of statins (n = 173). Current users of statins were being treated with atorvastatin (n = 14), simvastatin (n = 10), rosuvastatin (n = 6), or lovastatin (n = 2). Past users of statins had been treated with atorvastatin (n = 16), simvastatin (n = 12), rosuvastatin (n = 7), or lovastatin (n = 1). The majority (n = 30) of the current users of statins had also used statins in the past. Table 2 shows the bivariate analysis for the use of statins (current or past). Differences in age and disease duration were observed in both current and past users of statins. The past use of statins was associated with older age and higher disease duration compared to nonuse (61.3 [10.8] years vs. 55.8 [13.9] years, p = 0.026, and 13.5 [10.1] years vs. 9.7 [9.2] years, p = 0.028, respectively). Furthermore, current statins users, compared to nonusers, tended to be older (60.6 [10.9] years vs. 56.1 [13.9] years, p = 0.086) and have had longer disease duration (13.3 [9.9] years vs. 9.9 [9.4] years, p = 0.058). As expected, comorbid conditions such as arterial hypertension, coronary artery disease, and dyslipidemia were associated with both the current and the past use of statins ($p<0.05$). A tendency toward lower HAQ scores (0.9 [0.8] vs. 1.1 [0.8], p = 0.074) or higher functional status was observed in current users of statins, whereas no such association was observed for the past use of statins (1.0 [0.8] vs. 1.1 [0.8], p = 0.643). There were no associations with disease activity in terms of current or past use of statins. In addition, no associations with RA manifestations were found with regard to the use of statins (current or past) with ESR, patients' global health and pain assessments, and physicians' global health, functional impairment, and physical damage assessments.

In the multivariate analysis (Table 3), after adjusting for age, disease duration, arterial hypertension, coronary artery disease, and dyslipidemia, the current use of statins was associated with lower HAQ scores [OR 0.42 (CI 95%, 0.22-0.80)]; thus, with higher functional status.

Discussion

In search of alternative treatments to improve the outcomes of patients with RA and taking into account the increasing amount of literature demonstrating the immunomodulatory and anti-inflammatory effects of statins, we examined a group of Puerto Rican patients with RA to evaluate whether the use of statins could have an impact on their disease activity and functional status. We found that statins use was associated with a higher functional status in our population of RA patients. However, no association was observed between the use of statins and disease activity.

Statins have been demonstrated to have anti-inflammatory properties in animal models and human cell culture studies (3-7, 15). However, the clinical benefits of statins with regard to disease activity and function in RA patients remain controversial. The largest studies performed to assess the effects of statins in RA patients did not show any clinical benefits (16-17). These studies were based on a United States insurance-claims database and had oral steroids use as a surrogate marker of inflammation. There were no direct markers of disease activity or severity for analysis. Conversely, in the first clinical trial designed to study the effects of statins on RA (TARA), a clinically apparent effect was demonstrated (18). The TARA study was a double-blind,

placebo-controlled trial in 116 RA patients on standard therapy in which atorvastatin (40 mg/day) was added as an adjuvant. After 6 months, swollen joint count, DAS28 scores, and ESR and C-reactive protein (CRP) levels declined in patients receiving atorvastatin. In our study, these parameters of disease activity did not reach statistical significance.

The immunomodulatory effects of statins in RA patients have been further evidenced in 3 small clinical trials (19-21). Thirty patients with early RA were randomly assigned in an unblinded fashion to a group receiving methotrexate and prednisone (n = 15) or to a group receiving those 2 drugs plus atorvastatin (40 mg/day) (19). After 6 months of therapy, a significant suppression of acute phase reactants and marked reduction in disease activity was seen in the atorvastatin group. Another study was conducted in 15 patients with RA receiving treatment with methotrexate; simvastatin (40 mg/day) was given to 10 patients and chloroquine was given to 5 patients (20). After 8 weeks, the majority (9/10) of patients receiving simvastatin showed an ACR50 or better response; in contrast, that clinical response was not observed in patients who received chloroquine. Finally, one study assessed the efficacy of low-dose simvastatin (10 mg/day) for 12 weeks in 24 RA patients (21). Clinical improvement was reflected in ACR20 and 50 responses of 62% and 38%, respectively, as well as in decreases in ESR and CRP levels, and peripheral blood Th1/Th2 and CD4/CD8 ratios in the simvastatin-treated patients.

Table 2. Association of the use of statins with demographic features, lifestyle-related behaviors, clinical manifestations, disease activity, comorbidities, and functional status of rheumatoid arthritis patients

Variable	Current use of statins			Past use of statins		
	Yes (n = 32)	No (n = 177)	p-value	Yes (n = 36)	No (n = 173)	p-value
Age at study visit, mean years (SD)	60.6 (10.9)	56.1 (13.9)	0.086	61.3 (10.8)	55.8 (13.9)	0.026
Disease duration, mean years (SD)	13.3 (9.9)	9.9 (9.4)	0.058	13.5 (10.1)	9.7 (9.2)	0.028
Gender, % female	81.3	84.2	0.679	80.6	84.4	0.570
Alcohol use, %	3.1	4.0	0.822	2.8	4.1	>0.999
Smoking, %	9.4	9.0	0.952	8.3	9.3	>0.999
Exercise, %	21.9	18.1	0.612	16.7	19.1	0.736
Joint deformities, %	21.9	18.1	0.612	22.2	17.9	0.547
Joint surgeries, %	6.1	18.6	0.738	14.3	19.1	0.504
Extra-articular manifestations, %	62.5	64.4	0.836	66.7	63.6	0.726
ESR, mean mm/hr (SD)	26.2 (15.0)	32.9 (24.8)	0.318	28.5 (17.3)	32.5 (24.7)	0.699
DAS28, mean score (SD)	3.5 (1.6)	3.6 (1.7)	0.833	3.8 (1.7)	3.6 (1.7)	0.544
BMI, mean kg/m2 (SD)	29.3 (6.6)	27.7 (5.9)	0.186	28.4 (6.6)	27.9 (5.9)	0.647
Type 2 diabetes mellitus, %	15.6	11.3	0.552	13.9	11.6	0.777
High blood pressure, %	71.9	52.5	0.043	75.0	51.5	0.010
Coronary artery disease, %	15.6	4.6	0.033	19.4	3.5	0.002
Dyslipidemia, %	93.8	43.5	<0.001	94.4	42.2	<0.001
Corticosteroid use, %	81.3	77.4	0.629	83.3	76.9	0.509
DMARDs use, %	96.9	96.6	0.935	97.2	96.5	>0.999
HAQ score, mean score (SD)	0.9 (0.8)	1.1 (0.8)	0.074	1.0 (0.8)	1.1 (0.8)	0.643
Patient's global assessment, mean mm (SD)	39.2 (35.7)	39.9 (31.8)	0.915	44.1 (35.7)	38.8 (31.7)	0.375
Patient's pain assessment, mean mm (SD)	38.5 (33.2)	40.3 (32.1)	0.781	40.7 (33.2)	39.8 (32.0)	0.881
Physician's global assessment, mean mm (SD)	17.7 (19.9)	19.9 (22.9)	0.604	20.7 (23.4)	19.4 (22.3)	0.746
Physician's functional impairment assessment, mean mm (SD)	22.9 (23.3)	22.0 (23.8)	0.850	26.8 (26.1)	21.2 (23.1)	0.200
Physician's physical damage assessment, mean mm (SD)	15.8 (19.1)	18.6 (23.6)	0.527	16.7 (22.7)	18.4 (23.0)	0.689

SD: Standard deviation; BMI: Body mass index; CABG: Coronary artery bypass grafting; DMARDs: Disease-modifying anti-rheumatic drugs; DAS28: Disease Activity Score; ESR: Erythrocyte sedimentation rate; HAQ score: Health Assessment Questionnaire

Table 3. Association between the current use of statins and HAQ score in bivariate and multivariate models

Variable	Bivariate model OR (CI 95%)	Multivariate model* OR (CI 95%)
Functional status (HAQ score)	0.64 (0.39, 1.05)	0.42 (0.22, 0.80)

*Adjusted by age, disease duration, high blood pressure, coronary artery disease, and dyslipidemia. OR: Odds ratio; CI: Confidence interval

Although our study did not demonstrate a significant impact for the use of statins on disease activity parameters, the HAQ scores were lower in patients currently using statins than they were in nonusers. It is plausible that in an interventional study, one in which not only is the sample size increased but also the dose and period of exposure to statins are controlled, the impact on disease activity and functional status measures could be better judged.

There are limitations to our study. First, it had a small sample size; in particular, the number of patients who were taking statins at the time of their study visits was quite low (32/209), thus limiting our ability to analyze the impact of this medication on our population of RA patients. Second, this work has the limitations inherent to any cross-sectional study. The ascertainment of some clinical data was performed by record review; thus, critical information was not available for all patients. Third, we did not determine the actual length of treatment with statins or evaluate any other periods of time besides those corresponding to current (within the last month) and past use of statins. Perhaps, longer periods of exposure would have

a stronger association with RA outcome measures. Finally, the study was performed in a group of Hispanics from Puerto Rico evaluated at a tertiary hospital in San Juan, Puerto Rico; thus, our results may not necessarily reflect those of other ethnic groups.

In summary, although no association was found between the use of statins and the parameters of disease activity in this group of RA patients, the current use of statins was associated with a higher functional status. Interventional and longitudinal studies in larger populations are necessary to further elucidate the immunomodulatory benefits and clinical impact of statins in RA patients.

Resumen

Objetivo: Las estatinas tienen propiedades antiinflamatorias e inmunomoduladoras. Siendo artritis reumatoide (AR) una enfermedad inflamatoria, evaluamos si existe una asociación del uso de estatinas con la actividad de la enfermedad y función física en un grupo de pacientes con AR. Métodos: Se realizó un estudio transversal en 209 puertorriqueños con AR (según la clasificación de del Colegio Americano de Reumatología de 1987). Se determinaron las características demográficas, estilos de vida, actividad de la enfermedad (utilizando el *Disease Activity Score 28*), comorbilidades, índice de discapacidad (utilizando el *Health Assessment Questionnaire*), terapia farmacológica y medidas globales de los pacientes y los médicos utilizando escalas análogas visuales. Los datos fueron evaluados utilizando análisis univariado, bivariado y regresión logística múltiple. Resultados: La edad promedio (desviación estándar, DE) de la población estudiada al momento del estudio fue de 56.8 (13.5) años (rango: 24-86 años); 175 (83.7%) pacientes eran mujeres. El promedio (DE) de la duración de la enfermedad fue de 10.4 (9.5) años (rango: 0.0-44.0 años). Treinta y dos (15.3%) pacientes usaban estatinas al momento de la visita del estudio mientras que 36 (17.2%) usaron estatinas en el pasado. En el análisis multivariado, el uso presente de estatinas se asoció a una mejor función física (odds ratio 0.42, intervalo de confianza de 95% 0.22-0.88) luego de ajustar por la edad, duración de la enfermedad, hipertensión arterial, enfermedad coronaria y dislipidemia. No se encontró una asociación entre el uso presente o pasado de estatinas y la actividad de la enfermedad. Conclusión: En este grupo de pacientes con AR, el uso presente de estatinas se asoció a una mejor función física. Por otro lado, no se encontró asociación con la actividad de la enfermedad. Sin embargo, estudios prospectivos y con una mayor cantidad de pacientes son necesarios para confirmar estos hallazgos.

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