Beneficial Action of Statins in Patients with Rheumatoid Arthritis in a Large Observational Cohort

HIROSHI OKAMOTO, KYOKO KOIZUMI, SHIGEO KAMITSUJI, EISUKE INOUE, MASAKO HARA, TAISUKE TOMATSU, NAOYUKI KAMATANI, and HISASHI YAMANAKA

ABSTRACT. ***Objective.*** To analyze the possible beneficial effects of statins on the disease activity of patients with rheumatoid arthritis (RA) using a database from a large observational cohort study.

Methods. We studied a total of 7512 patients enrolled in a single-institute based prospective observational cohort of RA patients (IORRA); their information was collected biannually. In this study, cross-sectional data of 4152 patients (female 83.3%, average age 58.4 yrs) in October 2003 were analyzed (Mann-Whitney U-test).

Results. Among 4152 patients with RA, 279 (6.7%) were taking statins; patients taking statins had lower C-reactive protein (0.85 vs 1.24 mg/dl, respectively) and lower swollen joint counts (1.80 vs 2.55), but more frequently used corticosteroids (2.88 vs 2.40 mg/day) compared to patients not taking statins. Serum cholesterol level was closely related to the use of corticosteroids. Thus, an adjustment with the dose of corticosteroid was conducted; even taking account of the effects of steroids, RA disease activity indicated by patient's assessment for pain, physician's assessment, and swollen joint counts was significantly lower in patients with statins compared to those without.

Conclusion. This study indicates that statins have beneficial effects in reducing RA disease activity in the daily practice of rheumatology. (First Release April 15 2007; J Rheumatol 2007;34:964–8)

Key Indexing Terms:
RHEUMATOID ARTHRITIS STATINS DISEASE ACTIVITY

Rheumatoid arthritis (RA) is a systemic disease characterized by chronic inflammation in synovial tissue that results in destruction of multiple joints, and eventually leads to severe disability; thus, RA is a disease with poor prognosis in articular tissue.

Statin HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors have been widely used for treatment of hyperlipidemia[1], one of the major and most established risk factors of cardiovascular system events. Interestingly, McCarey, *et al* reported that data for the 28-joint Disease Activity Score (DAS28), a marker of inflammation indicators such as C-reactive protein (CRP) and swollen joint counts, were significantly improved in patients treated with atorvastatin in a randomized double-blind, placebo-controlled trial[2]. Effects of statins on RA have also been discussed recently[3,4]. Indeed, the antiinflammatory effects of statins have been reported in suppression of cytokine release and MHC class II expression *in vitro*, and also in inhibition of arthritis in a mouse model[5]. Effects on other mechanisms such as apoptosis of synovial cells and cytokine production have also been reported[6,7].

We would emphasize that experimental observations or results of experimental clinical studies should be confirmed in a real-life setting investigating possible beneficial effects for patients. Thus, it is useful to investigate the beneficial effect of statins in reducing RA disease

From the Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan.

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H. Okamoto, MD, PhD, Assistant Professor; K. Koizumi, MD, PhD, Instructor; S. Kamitsuji, PhD, Instructor; E. Inoue, BEng, Fellow; M. Hara, MD, PhD, Professor; T. Tomatsu, MD, PhD, Professor; N. Kamatani, MD, PhD, Professor, Chair, Institute of Rheumatology; H. Yamanaka, MD, PhD, Professor.

Address reprint requests to Dr. H. Okamoto, Institute of Rheumatology, Tokyo Women's Medical University, 10-22 Kawada-cho, Shinjuku, Tokyo 162-0054, Japan. E-mail: hokamoto@ior.twmu.ac.jp

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activity of patients in daily rheumatology practice. We analyzed the possible beneficial effects of statins on RA disease activity through a large observational cohort study in our institute.

MATERIALS AND METHODS

We established a prospective observational cohort of patients with RA at the Institute of Rheumatology, Tokyo Women's Medical University in October 2000[8]. We designate this cohort the IORRA study (Institute Of Rheumatology, Rheumatoid Arthritis). Patients with RA diagnosed by American College of Rheumatology (ACR) criteria[9] were registered, and their information was collected biannually (April to May and October to November) when the patient visited the outpatient unit for consultation. Informed consent of each patient was routinely taken each time.

Clinical information consisted of 3 components. (1) The physician's evaluation included number of tender joints, number of swollen joints, and a visual analog scale (VAS) of disease activity rated by the physician. (2) Information collected from patients included VAS for pain, VAS for general health disability level using the Japanese version of the Health Assessment Questionnaire (JHAQ)[8], height, body weight, comorbidity in the last 6 months, and information on drugs taken during the period. Patients were asked by the attending physician to answer these questions by filling out the questionnaire at home and were instructed to mail it back in a prestamped envelope within 2 weeks of their clinic visit. (3) The third part collected patients' laboratory data, including CRP levels, erythrocyte sedimentation rate (ESR), blood counts, transaminases, and serum cholesterol and urinalysis. Data collected from each section was integrated into one database for analysis. The DAS28 was calculated according to the original method[10].

A total of 7512 patients were enrolled into this study. In all phases of the study, more than 99% of RA patients in our institute were enrolled and more than 98% returned the questionnaire. Thus, patient selection bias is considered to be small, if any. The ethical committee of Tokyo Women's Medical University approved the study.

In this study, the dataset of 4152 patients with RA from the 7th phase of the IORRA cohort in October 2003 was analyzed. Subsets of the ACR core set, i.e., number of tender or swollen joints, VAS score, HAQ score, and CRP, were used to determine the severity of RA. To study the clinical improvement of RA activity, the DAS28 and the ACR preliminary criteria for improvement (ACR20) were used[11,12]. Changes in tender joint counts, swollen joint counts, ESR, and CRP were calculated by comparison to those of the 6th phase of the IORRA cohort from April 2003. Statistical analysis was performed using the Mann-Whitney U-test and Kruskal-Wallis test.

RESULTS

Among the 4152 patients (female 83.3%, average age 58.4 yrs) in the dataset, 279 patients (6.7%) were taking statins, including pravastatin (n = 137, 49%, mean dose 6.4 mg/day), atorvastatin (n = 64, 23%, mean dose 17.3 mg/day), simvastatin (n = 50, 18%, mean dose 7.2 mg/day), and fluvastatin (n = 28, 10%, mean dose 12.5 mg/day). The clinical characteristics of patients taking statins and without statins are given in Table 1A.

Patients taking statins had significantly lower disease activity assessed by CRP, pain assessment, physician assessment, swollen joint count, and tender joint count; they were significantly older, had longer disease duration, and had significantly higher frequency of taking corticosteroids (odds ratio 1.48, 95% confidence interval 1.14–1.92), but not of taking methotrexate. Doses of corticosteroids were also significantly higher (Table 1B).

Table 1A. Relationship between disease activity and statin use in patients with RA. Swollen joint count is calculated as the difference between the swollen joint counts observed in the 7th IORRA data and those from the 6th IORRA data.

Disease Activity Variable	Statin Group, mean ± SD	No Statin Group, mean ± SD	p
CRP	0.85 ± 1.36	1.24 ± 1.74	< 0.0001
Pain VAS	27.32 ± 25.34	31.13 ± 26.89	< 0.05
Physician VAS	12.59 ± 12.10	15.89 ± 15.06	< 0.001
Swollen joint counts	1.80 ± 2.86	2.55 ± 3.50	< 0.0001
Tender joint counts	2.32 ± 4.10	2.87 ± 4.93	< 0.05
General VAS	29.86 ± 25.72	32.45 ± 25.77	> 0.05
DAS28	3.45 ± 1.12	3.57 ± 1.24	> 0.05
HAQ	0.75 ± 0.71	0.75 ± 0.74	> 0.05
JHAQ	0.79 ± 0.74	0.80 ± 0.77	> 0.05
Age, yrs	64.03 ± 9.46	57.99 ± 12.77	almost 0
RA disease duration, yrs	13.00 ± 9.39	11.73 ± 8.74	< 0.05

CRP: C-reactive protein, VAS: visual analog scale, JHAQ: Japanese Health Assessment Questionnaire.

Thus, the lower disease activity in patients taking statins may be affected by the greater use of corticosteroids compared to patients without statins. To confirm the relationship between corticosteroid dose and total cholesterol levels in serum of these patients, we divided patients into 3 groups by corticosteroid dose. The average serum cholesterol level was higher in the high-dose corticosteroid group (> 5 mg/day prednisone, n = 505, 213.63 ± 40.23 mg/dl) than that in the middle-dose corticosteroid group (1~5 mg/day prednisone, n = 1424, 207.11 ± 34.47 mg/dl) and in the low-dose group (0 or < 1 mg/day prednisone, n = 1957, 202.97 ± 34.96 mg/dl), indicating the steroid dose-dependent increase of the serum cholesterol level (Figure 1). Since patients taking statins had a higher frequency of corticosteroid use (62.0% vs 52.5% among those not taking statins), average total cholesterol of patients with statins (222.08 ± 33.80 mg/dl) is higher that those without statins (204.68 ± 35.53 mg/dl). The effect of corticosteroids on serum cholesterol levels was significant.

To minimize the effects of corticosteroids, we analyzed the effects of statin use and dose level of corticosteroid (Table 2). Even at the same dose level of corticosteroids, patients taking statins had several significantly lower measures of disease activity including patient's pain assessment, physician's assessment, and swollen joint counts; however, no statistical differences were noted in DAS28 or HAQ.

Table 1B. Comparison of usage of statin and usage of methotrexate (MTX) or prednisolone.

Variable	Statin use	No Statin		p
Dosage of steroid, mean ± SD	2.88 ± 3.67	2.40 ± 2.98		< 0.05
Usage of steroid (yes/no)	173/106	2032/1841	OR 1.48 95% CI 1.14, 1.92	< 0.01
Usage of MTX (yes/no)	140/139	1953/1920	OR 0.99 95% CI 0.77, 1.27	> 0.1

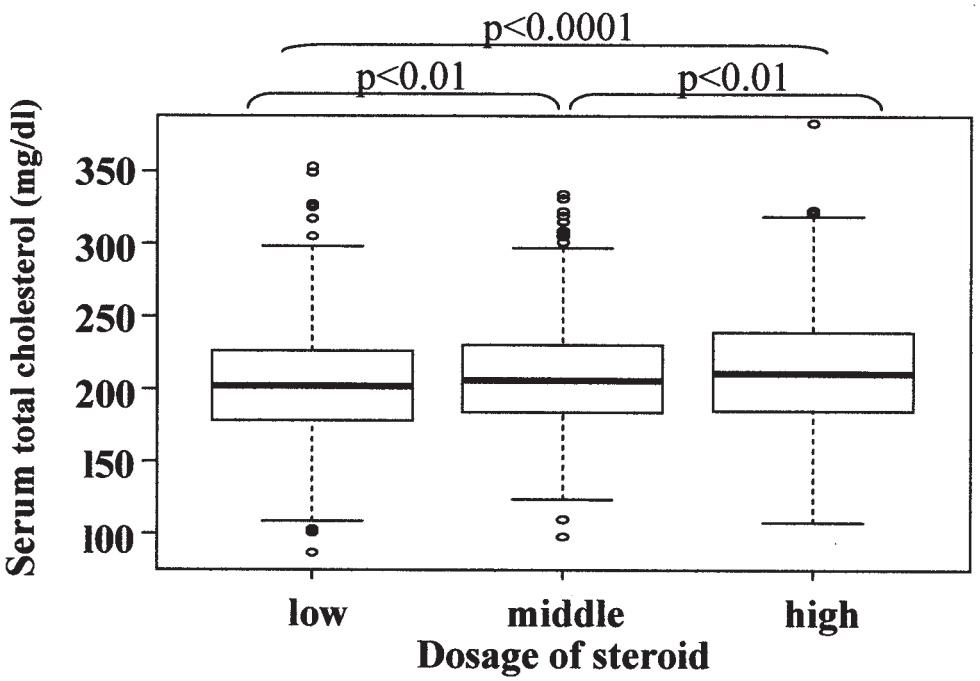

Figure 1. Comparison between serum cholesterol levels and dosage of steroids.

DISCUSSION

Using a dataset from a large observational cohort, IORRA, we have tried to eliminate the influence of corticosteroid use in this study: in patients with low or no steroid use, we observed some measures of inflammation that were significantly suppressed, but we did not observe significant differences in DAS28 or HAQ. We calculated the ACR20 in the dose level of steroid that was administered; however, no significant difference was observed (high-dose steroid group: $p < 0.05$; middle-dose steroid group: $p > 0.1$; low-dose steroid group: $p > 0.1$). Our results (Table 2) would be consistent with the theory that statins afford a modest reduction in inflammatory markers in RA. In combination with steroid therapy it would be difficult for statins to have a significant additional effect on inflammation above that provided by corticosteroids. This may explain why patients taking statins but not taking > 1 mg prednisolone a day seemed to have a more noticeable antiinflammatory effect. Considering that improvement of DAS28 and CRP was demonstrated in a randomized controlled trial using atorvastatin[2], this might be the limitation of our study design using the observational cohort.

The pleiotropic actions of statins, especially their ability to attenuate experimental inflammatory disease, have been discussed[5-7]. Although we failed to observe a dramatic effect of statins in anti-RA activity, our data showed some beneficial effects of statins on the disease activity of patients with RA and support the findings from double-blind, placebo-controlled studies and experimental observations[2-7] in daily rheumatology practice.

Table 2. Relationship between disease activity and statin use in RA patients of each group taking prednisone. High-dose group, > 5 mg/day; middle-dose group, 1–5 mg/day, low-dose group, < 1 mg/day. Δ tender joint counts: change in tender joint counts, Δ swollen joint count; change in swollen joint count, Δ ESR: change in ESR, Δ CRP: change in CRP, calculated by comparing data from the 6th phase of the IORRA cohort in April 2003.

		Dosage of Steroid		
		Low (129/2100) mean ± SD	Middle (105/1517) mean ± SD	High (45/535) mean ± SD
Pain VAS	Use	20.81 ± 23.18	31.46 ± 25.91	36.18 ± 25.70
	Non-use	25.29 ± 25.09	35.37 ± 26.89	42.45 ± 28.02
	p	0.02	0.18	0.16
Physician VAS	Use	9.33 ± 9.86	14.84 ± 12.84	16.73 ± 13.86
	Non-use	12.40 ± 12.83	18.12 ± 15.10	23.52 ± 18.78
	p	0.02	0.03	0.03
Tender joint count	Use	2.30 ± 4.83	1.93 ± 2.82	3.29 ± 4.29
	Non-use	2.48 ± 4.59	3.05 ± 4.84	3.87 ± 6.18
	p	0.26	0.01	0.96
Δ Tender joint count	Use	–0.27 ± 2.62	0.96 ± 4.24	0.36 ± 3.85
	Non-use	0.38 ± 3.72	0.35 ± 4.29	1.15 ± 5.98
	p	0.02	0.22	0.17
Swollen joint count	Use	1.16 ± 1.93	2.20 ± 3.29	2.69 ± 3.57
	Non-use	2.14 ± 3.21	2.73 ± 3.49	3.63 ± 4.29
	p	0.00	0.02	0.08
Δ Swollen joint count	Use	0.27 ± 0.93	0.30 ± 0.76	–0.80 ± 3.27
	Non-use	0.09 ± 0.98	–0.01 ± 1.21	–0.06 ± 1.46
	p	0.03	0.01	0.59
ESR	Use	29.7 ± 18.9	39.2 ± 24.2	36.1 ± 25.8
	Non-use	31.4 ± 22.6	37.2 ± 24.3	36.2 ± 24.7
	p	0.89	0.35	0.91
Δ ESR	Use	0.47 ± 10.3	1.43 ± 17.3	3.23 ± 26.3
	Non-use	–0.11 ± 13.6	–0.15 ± 15.7	2.54 ± 21.4
	p	0.79	0.38	0.63
CRP	Use	0.55 ± 0.72	1.01 ± 1.43	1.31 ± 2.18
	Non-use	0.93 ± 1.43	1.47 ± 1.88	1.77 ± 2.15
	p	0.01	0.01	0.02
Δ CRP	Use	–0.10 ± 1.36	–0.42 ± 3.10	–0.14 ± 1.56
	Non-use	–0.35 ± 2.05	–0.43 ± 2.81	–0.52 ± 2.83
	p	0.27	0.47	0.13
DAS28	Use	3.21 ± 1.03	3.57 ± 1.09	3.80 ± 1.26
	Non-use	3.33 ± 1.21	3.77 ± 1.20	3.96 ± 1.25
	p	0.33	0.08	0.56

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