Smoking, Smoking Cessation, and Disease Activity in a Large Cohort of Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** While cigarette smoking is the best-studied environmental factor contributing to rheumatoid arthritis (RA), no study to date has examined the influence of smoking cessation on disease activity. We examined this relationship in an observational cohort of patients with RA in the United States.
Methods. Patients enrolled in the Consortium of Rheumatology Researchers of North America registry (CORRONA) were stratified into never, former, and current smokers at enrollment. Current smokers were further stratified into continued and ceased smoking groups during their followup in the registry. The primary outcome was change in Clinical Disease Activity Index (CDAI) at last visit in a multi-variate, random-effects regression model accounting for multiple timepoints.
Results. At last visit, there was no significant change in CDAI between ceased smokers and continued smokers (coefficient –0.00091, SE 0.0033, p = 0.7834). The study did confirm prior cross-sectional studies that current smokers have worse disease activity than former or never smokers.
Conclusion. In the short term, smoking cessation did not appear to influence change in disease activity over time. (First Release March 15 2012; J Rheumatol 2012;39:904–9; doi:10.3899/jrheum.110852)

Key Indexing Terms:
RHEUMATOID ARTHRITIS   SMOKING   DISEASE ACTIVITY

Rheumatoid arthritis (RA) is a chronic inflammatory disease of multifactorial etiology. There is evidence of a role for both genetic factors and environmental factors in causation[1,2,3]. Cigarette smoking is the best-studied environmental factor contributing to RA. Recent studies demonstrated positive relationships between smoking, seropositive RA, and disease severity[4]. Additionally, smoking is related to rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA) isotype and titer[4].

To our knowledge, to date, no studies have examined the effect of smoking cessation on RA disease activity. We examined this relationship in an observational cohort of patients with RA in the United States.

MATERIALS AND METHODS

Population and cohort definitions. This analysis used data from patients enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) registry. Full details of the CORRONA registry have been reported[5]. In brief, patients with a diagnosis of RA, either new-onset or long-standing, are enrolled at an initial study visit. Clinical history, including duration of symptoms and date of diagnosis, is recorded, in addition to demographic information and RA medication history. A tender and swollen joint count is performed by a clinician. Patients are then seen every 3 months, although some patients may go longer between visits if deemed appropriate by their treating clinician. All data are collected by patient or physician report. Pertinent clinical history, tender and swollen joint counts, patient and physician global assessment, presence of erosions as reported by the treating rheumatologist, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are recorded at each visit, as are changes in RA medications. At each visit, patients are also asked if they are current, former, or never-smokers.

The study population included individual patients with smoking status information. Patients were stratified into never, former, and current smokers at their initial visit. Patients who reported current smoking at enrollment in the registry were further stratified into continued and ceased smoking groups during their followup in the registry. The study was approved by the institutional review boards (IRB) of participating academic sites, and a central IRB for community-based private sites.

Definition of smoking cessation. "Ceased smokers" were defined as patients who had reported current smoking who subsequently reported cessation of smoking on at least their last 2 consecutive CORRONA evaluations. A patient who noted smoking cessation only at their last followup visit was defined as

a continued smoker, as many patients who attempt to quit smoking will frequently resume smoking shortly afterward. Therefore, persistence of smoking cessation was required to define a patient as a "ceased smoker." In addition, patients who initially reported active smoking, then had multiple consecutive ceased smoking visits, then again reported active smoking, were classified as active smokers. Only patients who had continued cessation for multiple consecutive visits and including the last 2 followup visits were defined as ceased smokers. As the "ceased-smoker" definition required at least 3 CORRONA visits, the comparison group, "continued smokers," also required at least 3 visits. Patients from both groups were required to not be in remission as determined by Clinical Disease Activity Index (CDAI) at their index visit.

Matching. In order to control for duration of followup within CORRONA, ceased smokers were matched with continued smokers based on the total number of followup visits. All patients who noted active smoking at enrollment in CORRONA were analyzed; all continued smokers were matched with all ceased smokers. For most patients, study visits occurred at 3-month intervals.

Index visit. The index visit for ceased smokers was defined as the last visit while smoking status was reported as positive prior to the first reported cessation visit. Therefore, all patients were active smokers during the index visit. For example, if a patient had 5 CORRONA visits, and reported active smoking at visits 1 and 2, and smoking cessation at visits 3 through 5, the index visit was defined as visit 2. The index visit for continued smokers was determined by matching continued smokers with ceased smokers for total number of study visits. For example, if a continued smoker was matched with a ceased smoker where both had 5 visits and the index visit for the ceased smoker was the third visit, then the third visit for the continued smoker was used as the index visit.

Study outcomes. The primary outcome for the longitudinal analysis was change in CDAI score over time from the index visit. CDAI is a composite measure of RA disease activity consisting of the 28 tender joint count, 28 swollen joint count, patient global health score visual acuity scale, and physician global health visual acuity scale. The CDAI has been shown to correlate highly with the Disease Activity Score 28-joint count (DAS28)[6]. As the CDAI values had a skewed distribution, for the regression analysis they were transformed to square-root CDAI, which had a more normal distribution. The outcome variable is therefore the interaction between smoking cessation status and time.

Analysis. Chi-square statistics were performed for categorical variables, and analysis of variance for continuous variables. Index and last visit variables were assessed and controlled for in multivariate models, including age, sex, race/ethnicity, RF status, duration of disease, duration of followup, medication use [methotrexate (MTX) and prednisone usage and dose, other disease-modifying antirheumatic drug (DMARD) and biologic DMARD use]. Individual components of the CDAI were independently assessed, as were the modified Health Assessment Questionnaire, patient pain assessment, ESR, and CRP (when available). Assessment of change in CDAI over time was performed using the continued and ceased-smoker populations with a random-effects regression model, controlling for age, sex, RF status, race/ethnicity, disease duration, and medication use. The random-effects regression model assesses multiple covariates at each timepoint in followup, and calculates a coefficient for each. CDAI scores were transformed for this analysis to square-root CDAI to permit linear modeling. A sensitivity analysis random-effects regression model limiting followup to 2 years was also performed, as the number of patients at each timepoint beyond 24 months became significantly smaller, and could have had a disproportionate effect on the results. All statistics were analyzed using SAS version 9.1.

RESULTS

Figure 1 shows smoking status at enrollment of all patients in CORRONA at the time of this analysis, as well as how patients were stratified into continued and ceased smokers.

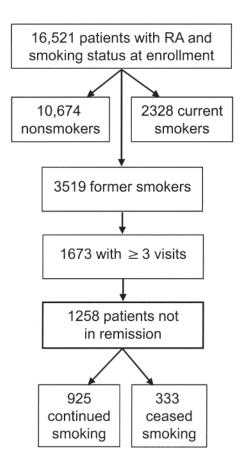Table 1 shows baseline characteristics of patients with RA

Figure 1. Smoking status at enrollment of all patients in the CORRONA registry at the time of this analysis. Patients were stratified into continued and ceased smokers. RA: rheumatoid arthritis.

included in the study stratified by smoking status. There were significant differences between never, former, and current smokers in sex, race/ethnicity, and mean age. Former and current smokers were more likely to be RF-positive than never-smokers; current smokers were more likely to be RF-positive than former smokers. Never and former smokers were more likely to be in remission or have low disease activity as measured by CDAI than current smokers (never-smokers, 17.2% and 31.0%, respectively; former smokers, 18.6% and 32.3%; current smokers, 13.1% and 25.8%; p < 0.0001). Mean CDAI and DAS28 scores at baseline were lowest among former smokers [13.5 (SD 12.9) and 3.5 (SD 1.6), respectively] and never-smokers had lower scores [14.2 (SD 12.8) and 3.7 (SD 1.6)] compared with current smokers [16.8 (SD 13.9) and 3.9 (SD 1.6)].

Table 2 shows the subgroup of current smokers, stratified into continued versus ceased smokers, with characteristics at index visit (while all were still smoking) and last visit. Of the 2328 current smokers at enrollment in CORRONA, 1258 had both 3 or more visits and followup data on smoking status and were included in this analysis. There were significant differences at index visit in age, disease duration, and duration of

Table 1. Baseline characteristics of CORRONA patients with rheumatoid arthritis at baseline visit, stratified by smoking status. For categorical variables the entries represent number of patients (percentages). For continuous variables entries represent mean (SD).

Characteristic	N	Never-smoker	N	Former Smoker	N	Current Smoker	p
Sex	10,673		3517		2328		
Female (%)		8373 (78.45)*†		2353 (66.90)*		1674 (71.91)	< 0.0001
Race	10,674		3519		2328		< 0.0001
Non-Hispanic White (%)		8670 (81.23)*†		3068 (87.18)*		1951 (83.81)	
Age (%)	10,657	57.68 (14.40)*†	3515	61.82 (11.95)*	2318	54.04 (11.59)	< 0.0001
RF-positive	5726		1813		1376		< 0.0001
Ever (%)		3870 (67.59)*†		1311 (72.31)*		1095 (79.58)	
CDAI	9654		3204		2135		< 0.0001
Remission (%)		1660 (17.19)*†		596 (18.60)*		279 (13.07)	
Low DAS		2991 (30.98)		1034 (32.27)		551 (25.81)	
Moderate DAS		2775 (28.74)		896 (27.97)		670 (31.38)	
High DAS		2228 (23.08)		678 (21.16)		635 (29.74)	
DAS28	4235		1472		979		0.0003
Remission (%)		1143 (26.99)*		434 (29.48)*		223 (22.78)	
Low DAS		595 (14.05)		217 (14.74)		139 (14.20)	
Moderate DAS		1692 (39.95)		560 (38.04)		380 (38.82)	
High DAS		805 (19.01)		261 (17.73)		237 (24.21)	
CDAI at 1st visit	9754	14.18 (12.80)*†	3255	13.50 (12.86)*	2151	16.80 (13.90)	< 0.0001
DAS28 at 1st visit	4246	3.67 (1.58)*	1477	3.60 (1.61)*	981	3.90 (1.62)	< 0.0001
Disease duration prior to enrollment, yrs	9968	10.01 (10.09)*	3379	9.86 (9.88)*	2220	7.60 (7.96)	< 0.0001
Duration of followup, mo	9968	23.95 (22.72)*†	3379	17.79 (18.23)*	2220	21.88 (21.90)	< 0.0001
CRP at first visit	3167	3.38 (9.83)	1187	3.10 (8.43)*	688	4.04 (8.69)	0.0704
ESR at first visit	4594	25.08 (22.20)	1601	25.64 (23.36)	1034	25.01 (21.83)	0.6764

* Statistically significant difference between former/never-smoker and current smoker. † Statistically significant difference between never-smoker and former smoker. RF: rheumatoid factor; CDAI: Clinical Disease Activity Index; DAS: Disease Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

followup within CORRONA between the 925 continued smokers and the 333 ceased smokers. There were no significant differences in sex, race/ethnicity, RF status, CRP, or ESR between the continued smokers and ceased smokers.

Disease activity at the index visit was significantly different between the 2 groups, measured by the CDAI [ceased, 12.9 (SD 12.1) vs continued, 16.5 (SD 13.1); p < 0.0001]. There were no differences at index visit in use of MTX, other traditional DMARD, prednisone or biologic DMARD, MTX or prednisone dose, history of erosions, or subcutaneous nodules (data not shown).

At last visit, mean CDAI scores were lower for ceased than for continued smokers [11.5 (SD 10.9) vs 14.3 (SD 12.6), respectively; p = 0.0002]. There was no significant difference in CRP levels or ESR.

Table 3 shows a random-effects regression model assessing change in CDAI score over time. In order to be included in the random effects regression model, all data at all data points had to be present; patients with missing data were excluded. Of the 1258 patients in the unadjusted analysis, 53 patients were eliminated due to missing data. The primary outcome variable, "effect of smoking on change in square-root CDAI over time in months," showed that over time, there was no significant difference in the square-root CDAI between patients who stopped smoking compared to patients who continued smoking (coefficient –0.00091, SE 0.0033, p = 0.7834). Baseline

disease activity adjusted for year of baseline visit was significantly lower in current smokers who ceased smoking (coefficient –0.345, SE 0.104, p = 0.0009). CDAI did not change significantly over time (coefficient –2.761, SE 2.591, p = 0.2866). The influence of smoking cessation was also not significant (coefficient –0.00091, SE 0.0033, p = 0.7834). Variables that significantly affected change in CDAI included biologic DMARD use (coefficient +0.569, SE 0.0849, p < 0.0001), use of MTX only (coefficient +0.255, SE 0.0928, p = 0.0064), year of index visit (coefficient –0.066, SE 0.0318, p = 0.0382), using only a traditional DMARD (coefficient +0.471, SE 0.134, p = 0.0008), prednisone use (coefficient –0.237, SE 0.066, p = 0.0004), and disease duration (coefficient –0.0207, SE 0.00446, p < 0.0001).

A sensitivity analysis limiting followup to 24 months, to eliminate the effect that few patients with greater followup could have, showed no difference from the primary model (coefficient –0.0045, SE 0.006, p = 0.4641).

DISCUSSION
This is the first study to examine the relationship between smoking cessation and change in disease activity in patients with RA enrolled in a longitudinal observational registry. In our study, smoking cessation did not appear to significantly influence disease activity over time. This analysis did confirm prior cross-sectional studies that current smokers have greater

Table 2. Baseline and last-visit characteristics of CORRONA patients with rheumatoid arthritis, current smokers stratified into continued versus ceased smoking. Cross-sectional analysis comparing continued to ceased smokers at index and at last followup visit.

Group	N	Ceased Smokers Mean (SD or %)	N	Continued Smokers Mean (SD or %)	p
Sex	333		925		0.4031
Female		238 (71.47)		683 (73.84)	
Race	331		921		0.9460
White		286 (86.40)		792 (85.99)	
Rheumatoid factor	195		531		0.1076
Positive		180 (92.31)		468 (88.14)	
Age	332	57.59 (12.12)	923	55.13 (11.44)	0.0014*
Disease duration, yrs	319	11.12 (9.43)	895	9.17 (8.82)	0.0013*
CORRONA duration of followup, yrs	333	3.82 (1.48)	925	2.60 (1.53)	< 0.0001*
Baseline CDAI	317	12.94 (12.07)	854	16.45 (13.14)	< 0.0001*
Baseline DAS28	131	3.68 (1.51)	367	3.95 (1.54)	0.0857
Baseline CRP	78	2.82 (9.20)	271	2.81 (5.92)	0.9986
Baseline ESR	138	25.53 (22.42)	394	25.34 (22.23)	0.9302
Last-visit CDAI	317	11.45 (10.90)	870	14.29 (12.62)	0.0002*
Last-visit DAS28	123	3.36 (1.46)	382	3.60 (1.54)	0.1200
Last-visit mHAQ (DI)	321	0.48 (0.51)	888	0.56 (0.53)	0.0194*
Last-visit VAS for physician disease activity assessment	333	18.09 (16.50)	922	21.30 (19.59)	0.0035*
Last-visit VAS for patient pain assessment	323	35.05 (26.48)	879	39.54 (27.12)	0.0099*
Last-visit VAS for patient global assessment	319	33.25 (26.58)	875	36.46 (26.50)	0.0656
Last-visit SJC	331	3.21 (4.95)	916	4.37 (5.87)	0.0005*
Last-visit TJC	331	2.98 (5.11)	917	4.05 (6.15)	0.0020*
Last-visit ESR	125	22.11 (19.92)	392	25.95 (23.57)	0.0746

* Statistical significance at 0.05 level. CDAI: Clinical Disease Activity Index; DAS: Disease Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; mHAQ: modified Health Assessment Questionnaire; DI: disability index; VAS: visual analog scale; SJC: swollen joint count; TJC: tender joint count.

disease activity and are less likely to be in states of remission or low disease activity than former or never-smokers.

Several studies have examined relationships among smoking and disease activity and severity; most had cross-sectional design and were performed in Europe[7,8,9,10,11]. These studies found smoking was associated with nodulosis and lower grip strength, and was variably related to disease activity, swollen joint count, radiographic erosions, ESR, and functional disability. North American studies found similar results[12,13,14].

We are unaware of any other study that reported on a cohort of patients with RA who are current smokers and explored differences between those who would quit smoking versus those who continued. There were some demographic differences between these groups; why these differences were associated with subsequent smoking cessation is unclear.

The most clinically important finding was the absence of the effect of smoking cessation on change in CDAI over time in longitudinal analysis. A strength of this model was the adjustment for multiple variables at multiple timepoints, including baseline disease activity, that varied based on year of enrollment and smoking status. A surprising finding was

the negative effect of use of biologics on CDAI values. However, this likely reflects that our study design did not measure change from predrug baseline assessments, but rather indicated prevalent use. Of note, recent studies reported that smoking was associated with decreased response to anti-tumor necrosis factor-α therapy and MTX[15,16,17].

There are several possible reasons why our study failed to reveal a relationship between smoking cessation and improvement in disease activity. One possibility is that this is a true finding, and that smoking cessation does not influence disease activity; once smoking has helped initiate the disease process, it may not play a role in the perpetuation of the disease. Of the 2328 patients who were current smokers at baseline, 1070 were not included in the analysis as they did not have sufficient visits within CORRONA. Had there been sufficient data on these patients, it is possible the results would have shown a benefit for smoking cessation. Since previous reports noted that the effect of smoking is greatest among patients who are ACPA-positive, another possibility is that an analysis stratified by ACPA status might show different results. The CORRONA dataset began before ACPA antibodies were routinely assessed in clinical practice, so for many patients, ACPA sta-

Table 3. Longitudinal random-effects regression models of the influence of smoking cesation on square-root CDAI score. Intercept represents baseline disease activity for patients who would continue smoking. Baseline disease activity prior to smoking cessation (reference: continued smoker) represents the difference in baseline disease activity for patients who would cease smoking compared to patients who continued to smoke.

| | N | CDAI with Interaction | | |
		Estimated Coefficient	SE	p
Subjects	1205			
Observations used	5691			
Intercept		136.23	63.789	0.0329
Baseline disease activity prior to smoking cessation (reference: continued smoker)		–0.345	0.104	0.0009
Change in square-root CDAI over time (months)		–2.761	2.591	0.2866
Effect of smoking on change in square-root CDAI over time (months) (reference: continued smoker)		–0.00091	0.00330	0.7834
Use of biologic (reference: none)		0.569	0.0849	< 0.0001
Time*biologic		–0.00137	0.00379	0.7185
Use of MTX only (reference: none)		0.255	0.0928	0.0064
Time*MTX		–0.0040	0.00434	0.3560
Time*index year		0.00137	0.00129	0.2893
DMARD only (reference: none)		0.471	0.134	0.0008
Time*DMARD		–0.00563	0.00627	0.3693
Prednisone (reference: none)		–0.237	0.0660	0.0004
Time*Prednisone		–0.0014	0.00288	0.6263
Age		–0.00539	0.00348	0.1214
Sex (reference: female)		0.0223	0.0881	0.8006
Race (reference: white)				
African American		0.247	0.174	0.1557
Asian		0.0144	0.362	0.9683
Hispanic		0.193	0.173	0.2635
Other		–0.0594	0.275	0.8288
Duration of followup, yrs		–0.0473	0.0277	0.0880
Disease duration, yrs		0.0207	0.00446	< 0.0001
Biologic starts (reference: none)[†]		NA	NA	NA
Biologic stops (reference: none)[†]		NA	NA	NA
DMARD-only starts (reference: none)		–0.175	0.121	0.1509
DMARD-only stops (reference: none)		–0.134	0.126	0.2903
MTX starts (reference: none)		–0.354	0.143	0.0147
MTX stops (reference: none)		–0.188	0.136	0.1702
Time*DMARD-only starts		0.00333	0.00559	0.5512
Time*DMARD-only stops		0.0126	0.00605	0.0371
Time*MTX starts		0.00318	0.00705	0.6515
Time*MTX stops		–0.00243	0.00647	0.7071

[†] There is no change of the status of using biologic during the followup period. The statistics associated with the variables are denoted not applicable (NA).

tus is unavailable. We look forward to performing that analysis in the future.

Additionally, smoking status in CORRONA is recorded as yes/no. If the patients who continued smoking had a smaller pack-year history than those who ceased, this might mitigate the difference in disease activity between the 2 groups. The overall duration of smoking cessation may not have been long enough to reveal an effect on RA disease activity. Finally, there was a fundamental difference in baseline disease activity between those who would cease smoking and those who continued smoking, comparing the last visit prior to smoking cessation. There may be fundamental differences between these 2 groups that go beyond sex, race, or RF status, but do relate to age, disease duration, duration of followup within CORRONA, or some other unassessed variable that may explain the differences. There also may be other reasons why

patients decide to quit smoking, including other health issues. These might include development of comorbid medical problems such as coronary artery disease, diabetes, hyperlipidemia, or hypertension, or development of greater concern for overall health. This concern could lead to other changes such as exercise, which might be associated with improvement in disease activity.

Strengths of our study include the prospective longitudinal design and the cohort size of the CORRONA registry. There are few other RA cohorts as large that include both smoking status and physician-derived outcome measures, including tender joint count and swollen joint count. Our study is appreciably larger than other investigations of the effects of smoking on RA outcomes.

Among the limitations, the observational design of the registry, like other registries, makes residual confounding a study

limitation. Second, these analyses are limited by absence of smoking duration and pack-years. That information was not recorded in earlier versions of the registry forms, and therefore was not available for analysis. Finally, some studies suggest smoking status is most germane among patients with the shared epitope and ACPA[18]. As ACPA status was not routinely measured in clinical practice until recently, it is not available for many patients enrolled in CORRONA prior to 2006.

This is the first study assessing the relationship between smoking cessation and RA disease activity. Smoking cessation does not appear to influence change in disease activity over time.

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