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ORIGINAL ARTICLE

Association of Tobacco Exposure and Reduction of Radiographic Progression in Early Rheumatoid Arthritis: Results From a French Multicenter Cohort

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Objective. **To investigate the initial response to treatment and risk of radiographic disease progression in current smokers (S), ex-smokers (EX), and nonsmokers (NS) in a prospective early arthritis cohort and to analyze the influence of smoking cessation on arthritis outcome.**

Methods. **The ESPOIR cohort is a prospective cohort study monitoring clinical, biologic, and radiographic data for patients with inflammatory arthritis lasting 6 weeks to 6 months. We examined the influence of smoking status on disease presentation (baseline characteristics) and therapeutic response at 1 year. Risk of structural progression at 12 months, defined as change in the modified Sharp/van der Heijde score ≥1, was analyzed by multivariate regression adjusted for potential confounders (age, sex, joint erosion at inclusion, educational level, positivity for rheumatoid factor or anti–cyclic citrullinated peptide 2 antibodies, and shared HLA–DRB1 epitope).**

Results. **A total of 813 patients were included; 641 (79%) fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism (EULAR) criteria for rheumatoid arthritis (RA). At inclusion, 138 (21.5%) were S patients, 168 (26.2%) were EX patients, and 335 (52.3%) were NS patients. Baseline acute-phase indicator values were significantly lower for S patients than EX and NS patients (mean ± SD erythrocyte sedimentation rate was 24.2 ± 18.2 mm/hour versus 33.4 ± 28.0 and 31.4 ± 25.0 [$P = 0.02$], respectively, and mean ± SD C-reactive protein level was 17.7 ± 28.0 mg/dl versus 28.5 ± 42.5 and 21.4 ± 29.0 [$P = 0.01$], respectively). Smoking status had no influence on Disease Activity Score in 28 joints, Health Assessment Questionnaire score, EULAR response, or use of disease-modifying antirheumatic drugs and biologic therapy in the first 12 months of followup ($P > 0.05$). The adjusted risk for structural disease progression was associated with active smokers (odds ratio 0.50 [95% confidence interval 0.27–0.93], $P = 0.028$). Sixteen patients had stopped smoking at 12 months, with no significant difference in observed outcomes from other patients.**

Conclusion. **In this large prospective cohort of patients with early arthritis, smoking status had no significant effect on disease activity and disability but did reduce 1-year radiographic disease progression. The antiinflammatory role of nicotine may explain the lower systemic inflammation and structural disease progression in current smokers with early RA.**

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes progressive joint destruction, disability, and premature death. Genetic and environmental risk factors are thought to be important in the pathogenesis of this complex inflammatory disease. Smoking is the best established environmental risk factor for the development of RA (1) and potential mechanisms are beginning to be understood. A recently published meta-analysis of 16 studies

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Significance & Innovations

- The relationship between the smoking status of patients with rheumatoid arthritis remains controversial, with opposite results showing for some authors a negative impact of cigarettes on patients' outcomes, but for others a potential benefit, at least from the rheumatologic condition point of view.
- Our study has several additional interests in this context, in that patients with recent, untreated inflammatory arthritis were prospectively followed up, and information on their smoking status collected in predefined standardized case report forms.
- No clear and relevant relationship between smoking status and therapeutic response could be found in our study.
- We showed a reduced radiographic progression in currently smoking patients as compared with nonsmokers.

investigating the association of tobacco consumption and risk of RA indicated that the risk was 2 times higher for males and 1.3 times higher for females for smokers than nonsmokers, respectively (1). For heavy smokers (≥20 pack-years), the risk was equally high for females and males (1). Furthermore, tobacco has been associated with the presence of extraarticular disease manifestations, including rheumatoid nodules (2,3), serum rheumatoid factor (RF) (2,4–6), and serum anti–citrullinated protein antibodies (ACPAs) (7–11). A 2-step model has been suggested for the pathogenesis of ACPA-positive arthritis (12); long-term exposure to tobacco smoke induces mechanisms that accelerate the citrullination of autoantigens in the lungs because the chronic inflammatory process is responsible for the switch of arginine to citrulline. Individuals who are smokers show increased citrullination in cells obtained from bronchoalveolar lavage (12). However, citrullination is not specific to RA and might occur in other types of arthritis. Thus, the production of ACPAs requires a specific genetic background and might be preferentially induced in individuals carrying the HLA–DRB1 shared epitope (12). In addition, some studies have suggested that smoking may influence RA disease severity (2,4,5,13–16), but results are highly conflicting (6,17–19).

Further investigations of the association of smoking status with presentation of arthritis, especially in the early phase, and outcome are required. We aimed to describe the association of smoking status and RA expression, disease activity, and disease severity (radiographic disease progression) in a cohort of patients with early inflammatory arthritis from the community. We also aimed to investigate the influence of smoking cessation on outcome of early arthritis.

PATIENTS AND METHODS

Patients. The ESPOIR cohort (20) is a prospective observational study of adults ages 18–70 years recruited from multiple regions across France under the umbrella of the French Society of Rheumatology. The patients were recruited if they had inflammatory arthritis of at least 2 swollen joints lasting for 6 weeks to 6 months and with potential to evolve into RA. Patients were included if they had not received disease-modifying antirheumatic drugs (DMARDs) or steroids. They were followed every 6 months during the first 2 years, then every year for at least 15 years.

We selected 641 patients who fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for RA at inclusion (21).

Clinical, laboratory, and radiologic features were compared at entry and at 6-month and 1- and 3-year followup periods. Clinical variables included total joint count for tenderness and swelling. To assess disease activity, the Disease Activity Score in 28 joints (DAS28) was calculated for each patient. Laboratory variables included erythrocyte sedimentation rate (ESR; mm/hour), C-reactive protein (CRP) level (normal <10 mg/liter), IgM and IgA RF (both enzyme-linked immunosorbent assay [ELISA; Menarini], both positive >9 IU/ml), and ACPA (ELISA; DiaSorin, positive >50 units/ml). Functional capacity was assessed by the Health Assessment Questionnaire (HAQ). Radiographs were obtained at baseline and annually thereafter. Radiographs of the hands and feet were evaluated by an author (CL), who applied the modified Sharp/van der Heijde total score (SHS) (22).

Clinical outcome was evaluated by EULAR response criteria, DAS28 remission (DAS28 score <2.6) at 1 year, and the HAQ disability index (DI). For this study, we calculated radiographic progression at 12 months, defined as a change ≥1 in the SHS.

Smoking history. Patients' smoking habits were evaluated at inclusion. Current smokers were those reporting active smoking. Ex-smokers were all patients who had stopped smoking before the first examination at inclusion. Nonsmokers reported no history of smoking at any time. Data on pack-years of smoking (1 pack-year is equivalent to 20 cigarettes a day for 1 year) were collected for current and ex-smokers at each visit.

Statistical analysis. Statistical analyses involved use of SPSS, version 15.0.

Comparison of baseline and 1-year characteristics by smoking status. Dichotomous outcomes and numerical variables were compared by chi-square and Whitney tests, respectively, between baseline and 1-year followup.

Evaluation of effect of smoking status on radiographic and clinical outcomes. Three logistic regression analyses were performed to examine the association of smoking status with: 1) structural disease progression (change in SHS ≥1; reliability analysis of radiographic scoring for the same sample of radiographs resulted in smallest detectable change score for 1 SHS unit [22]), 2) EULAR response at 1

year, and 3) DAS28 remission defined by a DAS28 score <2.6 at 1 year. The 3 logistic models included the potential confounders as follows: age, sex, erosiveness at inclusion, educational level, positivity for RF and ACPAs, and shared HLA–DRB1 epitope.

Evaluation of effect of smoking status and treatments. Chi-square or Fisher's tests were used to determine the following: 1) proportion of patients taking nonsteroidal antiinflammatory drugs (NSAIDs) at inclusion and 6 and 12 months in the 3 groups; 2) proportion of patients taking glucocorticoids at inclusion and 6 and 12 months in the 3 groups; 3) proportion of patients treated with conventional or biologic DMARDs at 12 months in the 3 groups; and 4) proportion of patients treated with biologic agents at 36 months in the 3 groups. The Mann-Whitney test was used to determine the following: 1) the number of days during which patients have used a dose of prednisone higher than 7.5 mg in the 3 groups during the first year, 2) the mean dose of prednisone at 12 months based on smoking status, and 3) the mean dose of methotrexate at 12 months in the 3 groups.

Nonparametric Kruskal-Wallis test was used to determine whether current smokers had more DMARD switches (including biologic agents) than ex- or nonsmokers during the first 3 years of monitoring. Data were analyzed by smoking status at baseline, then for patients whose smoking status did not change for 6 months during the first 3 years of monitoring.

Effect of smoking cessation. The effect of smoking cessation on acute-phase reactants (CRP level, ESR), DAS28 score, functional status (HAQ), and response to therapy was examined by bivariate analyses with Mann-Whitney or chi-square tests, then by logistic or linear regression after adjusting for the confounders mentioned previously.

RESULTS

Characteristics of patients. The main baseline characteristics of the 641 patients are in Table 1. The mean ± SD age was 48.43 ± 12.2 years and 77.8% were females. At inclusion, the mean ± SD number of swollen joints was 8.18 ± 5.51 and number of tender joints was 9.85 ± 7.16. The mean ± SD DAS28 score was 5.40 ± 1.23. In total, 48.8% of patients were seropositive for ACPAs and 64.1% for RF.

At baseline and at 6 months, 91.3% and 73.2% of patients, respectively, were receiving NSAIDs; at 6 months, 515 (85.83%) patients were receiving DMARDs, mostly methotrexate (62%), and 19 (2.96%) were receiving biologic therapy. At 1 year, 89.37% were receiving DMARDs and 7.8% biologic therapy; 56.55% and 48.1% were receiving NSAIDs and corticosteroid therapy, respectively.

Characteristics of patients by smoking status. At baseline, approximately one-half (48.7%) of patients had ever smoked; 138 were current smokers, 168 were past smokers, and 335 had never smoked (Table 2). During the first 12 months of the study, 16 patients stopped smoking. For patients who had ever smoked, the mean ± SD number of pack-years was 19.09 ± 16.46.

Table 1. Characteristics of patients with early rheumatoid arthritis who were smokers or nonsmokers*

	Value
Female sex, no. (%)	499 (77.8)
Age, years	48.43 ± 12.2
Disease duration, months	3.4 ± 1.7
Rheumatoid factor, no. (%)	411 (64.1)
Anti-CCP 2 positivity, no. (%)	313 (48.8)
Anti-CCP 2 level	605.41 ± 1,602.72
Cigarette smoking, no. (%)	
Current	138 (21.5)
Former	168 (26.2)
Never	335 (52.3)
Pack-year (20 cigarettes daily for 1 year), median ± SD	19.09 ± 16.46
Joint count	
Swollen (0–28)	8.18 ± 5.51
Tender (0–28)	9.85 ± 7.16
ESR (mm/first hour)	30.38 ± 24.80
CRP (mg/liter)	22.47 ± 33.8
DAS28	5.40 ± 1.23
Modified Sharp/van der Heijde score	6.12 ± 7.91
HAQ DI (range 0–3)	1.05 ± 0.69

* Values are the mean ± SD unless indicated otherwise. Anti-CCP = anti–cyclic citrullinated peptide; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; DAS28 = Disease Activity Score in 28 joints; HAQ = Health Assessment Questionnaire; DI = disability index.

At baseline, past and never smokers were older than current smokers ($P < 0.001$) (Table 2), but the groups did not differ in RF positivity or level, whatever the isotype (IgA or IgM), or in ACPA status or level. For the 313 ACPA-positive patients, the mean ± SD level of IgA RF was higher for smokers than never smokers (150.62 ± 98.39 for current smokers and 142.18 ± 74.42 and 118.44 ± 66.91 for ex-smokers and never smokers, respectively; $P = 0.004$) despite no difference in level of IgA RF by smoking status for all patients (n = 641) independent of ACPA status ($P = 0.24$).

Disease activity and smoking status. At baseline, the 3 groups did not differ in tender joint count, swollen joint count, or DAS28 score (Table 2). Patient global disease activity (by visual analog scale) was higher for current smokers than never or past smokers ($P = 0.042$). However, CRP level and ESR were lower for smokers than nonsmokers ($P = 0.013$ and $P = 0.020$, respectively). The difference between the groups decreased over time, with no difference in CRP level, ESR, tender or swollen joint score, patient global disease activity, or DAS28 score at 1 year.

Disease severity and smoking status. At baseline, the smoker groups did not differ in number of erosions or mean total radiologic score ($P = 0.870$ and $P = 0.363$, respectively). Radiographic progression at 1 year was not significantly different across the 3 groups (modified SHS change was 1.49 ± 4.7 for current smokers, 1.17 ± 2.96 for ex-smokers, and 1.90 ± 4.39 at 12 months for nonsmokers). At 3 years, radiographic progression was 9.0 ± 11.0; this outcome was similar across the 3 groups (modified

Table 2. Baseline clinical and laboratory findings for patients with early rheumatoid arthritis by smoking status*

	Current smokers (n = 138)	Ex-smokers (n = 168)	Never smokers (n = 335)	*P*
Age, years	44.65 ± 11.62	50.51 ± 10.98	49.13 ± 12.69	0.000
Tender joint count	9.78 ± 7.06	10.12 ± 7.20	9.74 ± 7.19	0.801
Swollen joint count	7.52 ± 5.24	8.48 ± 5.45	8.33 ± 5.65	0.272
Patient global disease severity (VAS, range 0–100)	66.04 ± 23.72	62.48 ± 24.89	60.11 ± 24.69	0.042
ESR, mm/first hour	24.16 ± 18.27	33.42 ± 27.97	31.37 ± 25.03	0.020
CRP, mg/dl	17.70 ± 27.96	28.45 ± 42.46	21.39 ± 28.99	0.013
DAS28	5.30 ± 1.16	5.48 ± 1.29	5.39 ± 1.22	0.516
Erosion positivity, %	25.00	25.16	27.03	0.870
Modified Sharp/van der Heijde score	5.50 ± 7.69	6.88 ± 8.80	5.98 ± 7.49	0.363
HAQ DI	1.07 ± 0.68	1.05 ± 0.68	1.04 ± 0.69	0.806
Ig RF positivity, %	64.50	64.28	63.88	0.991
IgM RF level	259.15 ± 1,005.87	100.52 ± 254.69	130.39 ± 519.86	0.368
IgA RF level	55.59 ± 115.45	43.06 ± 108.01	30.74 ± 62.38	0.240
Anti-CCP positivity, %	50	52.38	46.57	0.447
Anti-CCP level	712.86 ± 1,642.03	510.73 ± 1,150.63	608.63 ± 1,773.39	0.510
NSAIDs, %	93.48	91.67	90.15	0.495
Glucocorticoids, %	13.77	11.90	13.73	0.834

* Values are the mean ± SD unless indicated otherwise. VAS = visual analog scale; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; DAS28 = Disease Activity in 28 joints; HAQ = Health Assessment Questionnaire; DI = disability index; RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide; NSAIDs = nonsteroidal antiinflammatory drugs.

SHS score change was 8.2 ± 10.2 for current smokers, 9.6 ± 11.1 for ex-smokers, and 9.1 ± 11.2 for nonsmokers).

On multivariate analysis (Table 3), current smokers showed decreased risk of radiographic disease progression at 1 year as compared with nonsmokers (odds ratio [OR] 0.50, 95% confidence interval [95% CI] 0.27–0.91; P = 0.024). Other variables independently associated with radiographic disease progression were ACPA positivity, presence of erosions at baseline, male sex, and age, but not RF positivity or shared HLA–DRB1 epitope (Table 3).

When high titers of IgA or IgM RF (>3 times the upper limit of normal) were considered, they did not influence the risk of structural progression (OR 1.42, 95% CI 0.84–2.39, P = 0.19 for high titer IgA RF; OR 1.36, 95% CI 0.79–2.32, P = 0.26 for high titer IgM RF; and OR 1.49, 95% CI 0.85–2.60, P = 0.17 for high titer IgA RF or high titer IgM RF). When time-averaged CRP levels (mean values of CRP levels at baseline and months 6 and 12) were included in the logistic models in addition to the previously cited potential confounders, the active exposure to tobacco did not significantly influence any more radiographic progression (OR 1.72, 95% CI 0.91–3.25, P = 0.09). However, there was still a trend; since it cannot be considered as a baseline predictive variable of outcome, time-averaged CRP level is not usually included in the multivariate predictive models of RA outcome. Of note is that time-averaged CRP level did not influence structural progression either (OR 1.02, 95% CI 0.998–1.34, P = 0.08).

Table 3. Multivariable analysis for risk of structural progression in rheumatoid arthritis at 1 year*

	OR	95% CI	*P*
Age	1.02	1.00–1.04	0.04
Sex (male vs. female)	1.95	1.13–3.38	0.01
Shared HLA–DRB1 epitope (double vs. single or absent)	1.82	0.92–3.57	0.08
Education level			
High school (>3 years) vs. primary	0.73	0.31–1.69	0.45
High school 2°cycle (<3 years) vs. primary	0.84	0.39–1.83	0.66
High school 1°cycle vs. primary	1.43	0.64–3.21	0.38
Anti-CCP positive vs. negative	3.07	1.70–5.56	< 0.001
Ig RF positive vs. negative	1.82	0.95–3.48	0.07
Current smoker vs. never smoked	0.49	0.27–0.91	0.024
Ex-smoker vs. never smoked	0.57	0.32–1.02	0.057
Joint erosion vs. no erosion at inclusion	3.76	2.30–6.14	< 0.001

* OR = odds ratio; 95% CI = 95% confidence interval; anti-CCP = anti–cyclic citrullinated peptide; RF = rheumatoid factor.

The HAQ DI was not associated with smoking status at inclusion or at 1 year.

Clinical outcome at 1 year. At 1 year, 83% of patients showed good EULAR response and 37.1% showed DAS28 remission. Multivariate regression analyses did not reveal any association between smoking status and EULAR response or rate of DAS28 remission. Covariates independently associated with EULAR good response at 1 year included male sex (OR 2.53, 95% CI 1.24–5.17; $P = 0.01$) and double HLA–DRB1 shared epitope (OR 0.43, 95% CI 0.22–0.87; $P = 0.02$). Covariates independently associated with DAS28 remission at 1 year included male sex (OR 1.94, 95% CI 1.21–3.10; $P = 0.006$) and older age (OR 0.98, 95% CI 0.96–0.99; $P = 0.012$).

Drug therapy at 1 and 3 years. At 6 months, 71.2% of current smokers, 74.2% of past smokers, and 73.5% of never smokers received NSAIDs ($P = 0.83$) and 48.8%, 58.3%, and 43.9%, respectively, received glucocorticoids ($P = 0.35$ for current smokers versus no smokers). At 1 year, 37.3% of current smokers, 42.76% of past smokers, and 46.2% of never smokers, respectively, received NSAIDs ($P = 0.24$) and 50.8% of current smokers, 44.6% of past smokers, and 56.1% of never smokers, respectively, received glucocorticoids ($P = 0.06$). Similarly, the mean ± SD number of days when patients had used a prednisone dose >7.5 mg during the first year was similar between the 3 groups (35.9 ± 72.3 days for current smokers, 49.5 ± 81.1 days for ex-smokers, and 40.8 ± 75.9 days for never smokers; $P = 0.22$).

At 12 months, the mean ± SD dose of prednisone in the 3 groups was also not significantly different between groups (3.0 ± 4.7 mg for current smokers, 3.5 ± 4.1 mg for ex-smokers, and 3.4 ± 6.3 mg for never smokers; $P = 0.69$).

At 12 months, 51.8% of patients were treated with methotrexate; the mean ± SD dose was similar in the 3 groups (13.3 ± 4.0 mg for current smokers, 13.2 ± 3.9 mg for ex-smokers, and 13.1 ± 4.0 mg for never smokers; $P = 0.97$).

Over the first year of followup, 89.37% of patients used DMARDs and 7.80% of patients used biologic agents. A similar proportion of patients in the 3 groups have received DMARDs (90.3% of current smokers, 87.0% of ex-smokers, and 90.2% of never smokers; $P = 0.51$) and biologic agents (8.0% of current smokers, 9.5% of ex-smokers, and 6.9% of never smokers; $P = 0.57$)

At 36 months, a similar proportion of patients in the 3 groups have used biologic agents (11.3% of current smokers, 19.4% of ex-smokers, and 15.7% of never smokers; $P = 0.23$). The smoking status did not influence the number of therapies used.

Effect of discontinuing smoking on disease activity and severity. During the first year of the study, only 16 patients stopped smoking. This group did not differ in disease activity or severity scores from current smokers.

DISCUSSION

This is the first prospective study evaluating the effects of tobacco use on disease activity and severity of early arthritis in patients fulfilling the 2010 ACR/EULAR criteria for RA. Furthermore, this work involves a large national cohort, so our investigation of 641 patients from the community is representative of patients seen in everyday life because recruitment was by private rheumatologists working with 16 university departments of rheumatology.

Smoking is a well-established environmental risk factor for the development of RA, mainly seropositive RA, but its effects on RA severity are highly controversial. In this large observational study, we found that, at baseline, current smokers had significantly lower CRP levels and ESR than nonsmokers and ex-smokers, despite the fact that disease activity (DAS28, swollen joints, and tender joints) was similar across the groups. At 1 year, the 3 smoker groups did not differ in inflammatory clinical or biologic variables, disease activity, or functional capacity by the HAQ DI. At 1 year, radiographic disease progression was lower for current smokers than nonsmokers.

Other studies have found a protective effect of smoking on RA outcome. Finckh et al demonstrated a significant inverse dose-response relationship between current smoking intensity and radiographic disease progression (18). Wolfe and Zwillich found past or present smoking protective for total joint replacement with RA (23). In a longitudinal study, Harrison et al found that current smokers had significantly fewer swollen joints over time (6).

Other studies did not observe any influence of smoking status on radiographic outcome (15,19) or a negative association between smoking and radiographic scores (2,5,16). However, these conflicting reports were based on patients with established disease and had important weaknesses. In the study by Wolfe (5), the effect was detected by nonlinear models and only in patients with a long smoking history. For the cohort in the study by Saag et al (16), the association between smoking and radiographic score disappeared after adjustment for RF. In addition, all studies demonstrating a significant association of smoking and radiographic joint damage were cross-sectional analyses (2,4,13,16), which can misclassify exposure (smoking status). Patients with nonsevere illness (does not require a hospital followup) and very severe disease (patients are deceased or cannot participate) were under-represented. Furthermore, cross-sectional studies cannot establish the temporality of events, which limit their ability for causal inferences.

Most studies did not find any association of smoking status and HAQ DI score (5,6,15,18). Three studies found HAQ DI scores higher for patients who had ever smoked (2,14) or current smokers (13) than nonsmokers. However, the HAQ DI is linked to social deprivation, which is also associated with cigarette smoking. Therefore, smoking may be associated with the HAQ DI in established disease because of a common association with psychosocial variables. Moreover, the HAQ DI depends on disease duration because it predominantly reflects joint inflammation in early disease and joint damage in long-standing disease (24). Similar to our results, in the study by Hyrich et al

(25), smoking status was not a predictor of clinical remission.

These results suggest that the discrepancies between published studies of the effect of smoking on RA severity may be related to study design (cross-sectional versus longitudinal), patient characteristics (established versus early RA), and other methodologic issues.

Smoking has been mainly associated with IgM RF status, but recent studies showed the association of smoking and seropositive RA related only to IgA RF status (19,26). This finding is consistent with our results in the subgroup of patients who were positive for ACPAs. IgA RF positivity was also more frequently observed in current than former smokers. The association of smoking and IgA RF status is attractive because IgA antibodies are important in mucosal immunity. Thus, smoking may activate or stimulate the immune system of the airway mucosa, thus leading to increased production of IgA RF. The B cells activated in the bronchoalveolar tract are prominent producers of IgA antibodies, and the detection of organized bronchus-associated lymphoid tissue involved in the generation of IgA-producing cells is more frequent in smokers than nonsmokers (27).

Most studies have considered smoking a pejorative factor for response to RA treatments (14,15,28–30) and some studies suggest that only some therapies may be influenced by tobacco (25).

Similar to the study by Harrison et al (6), we did not find any difference between smokers and nonsmokers in DMARD use and response. The association of smoking and poor response was due to increased frequency or rate of RF and ACPA. Our results may differ from other findings because our population is a true early RA population. One advantage of our work is that for the second part of the analysis concerning number of treatments at the 3-year followup, the patients had not changed smoking status for more than 6 months over the study.

Only one other study investigated the effect of smoking cessation or reduced tobacco consumption on early RA (31). Among the 16,251 RA patients enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) registry, 318 of whom stopped smoking after enrollment, the proportion of patients in disease remission at followup was higher for those who stopped smoking than those who were still smoking. After adjusting for baseline biologic DMARD use, the association with the rate of remission was higher for patients who stopped smoking as compared with those who continued to smoke (OR 1.49, 95% CI 1.05–2.0; $P = 0.025$). In our study, only 16 patients stopped smoking at 12 months, with no significant difference in observed outcomes from those who continued to smoke. The low number of patients and the short-term followup may explain these discrepancies.

The finding that radiographic disease progression and systemic inflammation were lower for smokers than nonsmokers was not expected. Smoking could have an antiinflammatory effect and suppress the immune response. Immune dysfunction has been reported in smokers, with abnormalities in T lymphocytes, reduced natural killer cells, and depressed humoral and cell-mediated immunity (32). Spector and Blake proposed that smoking might reduce the number of antigen-presenting cells and therefore improve inflammation (33).

Some evidence suggests that components of cigarette smoke may influence the release of cytokines; nicotine was found to inhibit the production of tumor necrosis factor α (TNFα) (34,35), interleukin-6 (IL-6) (36,37), IL-2 (34,35), and IL-10 (35). The inhibitory effects of cigarette smoking were attributed to nicotine, hydroquinone (the phenolic compound in cigarette tar), carbon monoxide in smoke, and the breakdown products of nicotine (37). Some of the inhibitory effects of nicotine have been attributed to its effect on the α7 nicotinic actylcholine receptor found in macrophages, T cells, and B cells (38). Activation of this receptor reduced the production of the proinflammatory cytokines TNFα, IL-1β, and IL-6 and suppressed reactions of Th1 and Th17, but not Th2 (38). In a rat model of human RA, nicotine pretreatment worsened arthritis symptoms, but nicotine posttreatment suppressed the disease (39). Another potential pathway through which nicotine can exert antiinflammatory properties is spinal activation of the primary afferent nociceptor, which inhibits plasma extravasations in animal models of arthritis (40).

In conclusion, our prospective cohort of early RA patients revealed lower baseline biologic markers and structural disease progression over 1 year for patients who were active smokers than nonsmokers. These data may be explained by the antiinflammatory property of nicotine on the cholinergic receptor α7 and its activation of spinal nociceptors. Smoking may be a risk factor for the initiation of RA but not the perpetuation of disease activity or progression. Unfortunately, smoking cessation cannot be recommended to prevent severe outcome in early RA patients.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Combe had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1. Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, et al, Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2010;69:70–81.
2. Mattey DL, Hutchinson D, Dawes PT, Nixon NB, Clarke S, Fisher J, et al. Smoking and disease severity in rheumatoid arthritis: association with polymorphism at the glutathione S-transferase M1 locus. Arthritis Rheum 2002;46:640–6.
3. Nyhall-Wahlin BM, Petersson IF, Nilsson JA, Jacobsson LT, Turesson C. High disease activity disability burden and smoking predict severe extra-articular manifestations in early rheumatoid arthritis. Rheumatology (Oxford) 2009;48:416–20.
4. Papadopoulos NG, Alamanos Y, Voulgari PV, Epagelis EK, Tsifetaki N, Drosos AA. Does cigarette smoking influence disease expression, activity and severity in early rheumatoid arthritis patients? Clin Exp Rheumatol 2005;23:861–6.
5. Wolfe F. The effect of smoking on clinical, laboratory, and radiographic status in rheumatoid arthritis. J Rheumatol 2000; 27:630–7.
6. Harrison BJ, Silman AJ, Wiles NJ, Scott DG, Symmons DP. The association of cigarette smoking with disease outcome in patients with early inflammatory polyarthritis. Arthritis Rheum 2001;44:323–30.
7. Linn-Rasker SP, van der Helm-van Mil AH, van Gaalen FA, Kloppenburg M, de Vries RR, le Cessie S, et al. Smoking is a risk factor for anti-CCP antibodies only in rheumatoid arthritis patients who carry HLA-DRB1 shared epitope alleles. Ann Rheum Dis 2006;65:366–71.
8. Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA–DR (shared epitope)–restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 2006;54:38–46.
9. Van der Helm-van Mil AH, Verpoort KN, Breedveld FC, Huizinga TW, Toes RE, de Vries RR. The HLA–DRB1 shared epitope alleles are primarily a risk factor for anti–cyclic citrullinated peptide antibodies and are not an independent risk factor for development of rheumatoid arthritis. Arthritis Rheum 2006;54:1117–21.
10. Verpoort KN, Papendrecht-van der Voort EA, van der Helm-van Mil AH, Jol-van der Zijde CM, van Tol MJ, Drijfhout JW, et al. Association of smoking with the constitution of the anti–cyclic citrullinated peptide response in the absence of HLA–DRB1 shared epitope alleles. Arthritis Rheum 2007;56: 2913–8.
11. Lee HS, Irigoyen P, Kern M, Lee A, Batliwalla F, Khalili H, et al. Interaction between smoking, the shared epitope, and anti–cyclic citrullinated peptide: a mixed picture in three large North American rheumatoid arthritis cohorts. Arthritis Rheum 2007;56:1745–53.
12. Klareskog L. Rheumatoid arthritis. Lancet 2009;373:659–72.
13. Masdottir B, Jonsson T, Manfredsdottir V, Vikingsson A, Brekkan A, Valdimarrsson H. Smoking, rheumatoid factor isotypes and severity of rheumatoid arthritis. Rheumatology (Oxford) 2000;39:1202–5.
14. Mattey DL, Brownfield A, Dawes PT. Relationship between pack-year history of smoking and response to tumor necrosis factor antagonists in patients with rheumatoid arthritis. J Rheumatol 2009;36:1180–7.
15. Westhoff G, Rau R, Zink A. Rheumatoid arthritis patients who smoke have a higher need for DMARDs and feel worse, but they do not have more joint damage than non-smokers of the same serological group. Rheumatology (Oxford) 2008;47:849–54.
16. Saag KG, Cerhan JR, Kolluri S, Ohashi K, Hunninghake GW, Schwartz DA. Cigarette smoking and rheumatoid arthritis severity. Ann Rheum Dis 1997;56:463–9.
17. Forslind K, Ahlmen M, Eberhardt K, Hafstrom I, Svensson B. Prediction of radiological outcome in early rheumatoid arthritis in clinical practice: role of antibodies to citrullinated peptides (anti-CCP). Ann Rheum Dis 2004;63:1090–5.
18. Finckh A, Dehler S, Costenbader KH, Gabay C. Cigarette smoking and radiographic progression in rheumatoid arthritis. Ann Rheum Dis 2007;66:1066–71.
19. Manfredsdottir VF, Vikingsdottir T, Jonsson T, Geirsson AJ, Kjartansson O, Heimisdottir M, et al. The effects of tobacco smoking and rheumatoid factor seropositivity on disease activity and joint damage in early rheumatoid arthritis. Rheumatology (Oxford) 2006;45:734–40.
20. Combe B, Benessiano J, Berenbaum F, Cantagrel A, Daures J, Dougados M, et al. The ESPOIR cohort: a ten-year follow-up of early arthritis in France: methodology and baseline characteristics of the 813 included patients. Joint Bone Spine 2007;74: 440–5.
21. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569–81.
22. Lukas C, Combe B, Ravaud P, Sibilia J, Landew R, van der Heijde D. Favorable effect of very early disease-modifying antirheumatic drug treatment on radiographic progression in early inflammatory arthritis: data from the Etude et Suivi des polyarthrites indifferenciees recentes (study and followup of early undifferentiated polyarthritis). Arthritis Rheum 2011; 63:1804–11.
23. Wolfe F, Zwillich SH. The long-term outcomes of rheumatoid arthritis: a 23-year prospective, longitudinal study of total joint replacement and its predictors in 1,600 patients with rheumatoid arthritis. Arthritis Rheum 1998;41:1072–82.
24. Drossaers-Bakker KW, de Buck M, van Zeben D, Swinderman AH, Breedveld FC, Hazes JM. Long-term course and outcome of functional capacity in rheumatoid arthritis: the effect of disease activity and radiologic damage over time. Arthritis Rheum 1999;42:1854–60.
25. Hyrich KL, Watson KD, Silman AJ, Symmons D. Predictors of response to anti-TNF-α therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford) 2006;45: 1558–65.
26. Mikuls TR, Hughes LB, Westfall AO, Holers VM, Parrish L, van der Heijde, et al. Cigarette smoking, disease severity and autoantibody expression in African Americans with recent-onset rheumatoid arthritis. Ann Rheum Dis 2008;67:1529–34.
27. Sokjer M, Jonsson M, Bodvarsson S, Jonsdottir I, Valdimarsson H. Selective increase of IgA rheumatoid factor in patients with gluten sensitivity. Acta Derm Venereol 1995;75: 130–2.
28. Wessels JA, van der Kooij SM, le Cessie S, Kievit W, Barerra P, Allaart CF, et al, for the Pharmacogenetics Collaborative Research Group. A clinical pharmacogenetic model to predict the efficacy of methotrexate monotherapy in recent-onset rheumatoid arthritis. Arthritis Rheum 2007;56:1765–75.
29. Saevarsdottir S, Wedren S, Seddighzadeh M, Bengtsson C, Wesley A, Lindblad S, et al. Patients with early rheumatoid arthritis who smoke are less likely to respond to treatment with methotrexate and tumor necrosis factor inhibitors: observations from the Epidemiological Investigation of Rheumatoid Arthritis and the Swedish Rheumatology Register cohorts. Arthritis Rheum 2011;63:26–36.
30. Soderlin M, Geborek P. Intensity of smoking (pack-years) is associated with poor therapy response in RA patients starting their first anti-TNF treatment: data from SSATG, a biologics register in southern Sweden [abstract]. Ann Rheum Dis 2010; Suppl 3:54.
31. Fisher MC, El-Taha M, Kremer JM, Peng C, Greenberg J. Smoking cessation and improvement in RA disease activity [abstract]. Arthritis Rheum 2008;58 Suppl:S610.
32. Arnson Y, Shoenfeld Y, Amital H. Effects of tobacco smoke on

immunity, inflammation and autoimmunity. J Autoimmun 2010;34:J258–65.
33. Spector TD, Blake DR. Effect of cigarette smoking on Langerhans' cells [abstract]. Lancet 1988;2:1028.
34. Kalayciyan A, Orawa H, Fimmel S, Perschel FH, Gonzalez JB, Fitzner RG, et al. Nicotine and biochanin A, but not cigarette smoke, induce anti-inflammatory effects on keratinocytes and endothelial cells in patients with Behçet's disease. J Invest Dermatol 2007;127:81–9.
35. Zoppini G, Faccini G, Muggeo M, Zenari L, Falezza G, Targher G. Elevated plasma levels of soluble receptors of TNF-α and their association with smoking and microvascular complications in young adults with type 1 diabetes. J Clin Endocrinol Metab 2001;86:3805–8.
36. Lindblad SS, Mydel P, Jonsson IM, Senior RM, Tarkowski A, Bokarewa M. Smoking and nicotine exposure delay development of collagen-induced arthritis in mice. Arthritis Res Ther 2009;11:R88.
37. McGilligan VE, Wallace JM, Heavey PM, Ridley DL, Rowland IR. Hypothesis about mechanisms through which nicotine might exert its effect on the interdependence of inflammation and gut barrier function in ulcerative colitis. Inflamm Bowel Dis 2007;13:108–15.
38. Nizri E, Irony-Tur-Sinai M, Lory O, Orr-Urtreger A, Lavi E, Brenner T. Activation of the cholinergic anti-inflammatory system by nicotine attenuates neuroinflammation via suppression of Th1 and Th17 responses. J Immunol 2009;183:6681–8.
39. Yu H, Yang YH, Rajaiah R, Moudgil KD. Nicotine-induced differential modulation of autoimmune arthritis in the Lewis rat involves changes in interleukin-17 and anti–cyclic citrullinated peptide antibodies. Arthritis Rheum 2011;63:981–91.
40. Miao FJ, Green PG, Benowitz N, Levine JD. Central terminals of nociceptors are targets for nicotine suppression of inflammation. Neuroscience 2004;123:777–84.