Effects of Smoking on Disease Activity and Radiographic Progression in Early Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To analyze the effects of cigarette smoking on disease activity and radiographic damage in patients with early rheumatoid arthritis (RA).

Methods. Study subjects were 156 patients with early RA (< 2 yrs). Disease activity, therapeutic response, and radiographic progression were compared in smokers and nonsmokers at 24 months.

Results. At baseline, ever-smokers had earlier disease onset and a closer association with the shared epitope (SE), but not more seropositive disease. No significant differences were observed in disease activity and European League Against Rheumatism therapeutic responses between smokers and nonsmokers. Multivariate analysis showed that baseline Larsen score, the HLA-DRB*04 genotype, being female, and current smoking were associated with radiographic progression.

Conclusion. In patients with early RA, smoking was associated with earlier disease onset and the SE. Smoking was an independent factor of radiographic progression. (J Rheumatol First Release Nov 1 2011; doi:10.3899/jrheum.110410)

Key Indexing Terms:
RHEUMATOID ARTHRITIS PROGNOSIS SMOKING RADIOGRAPHIC DAMAGE

Smoking is an accepted risk factor for rheumatoid arthritis (RA)[1], increasing the risk of seropositive RA (rheumatoid factor; RF) or anticitrullinated protein antibodies (ACPA). Recent studies suggest smoking is associated with a poor response to antirheumatic drugs[2]. However, the effect of smoking on disease activity, clinical course, and radiographic damage in early RA is unclear[3,4].

We analyzed the effects of smoking on disease activity, therapeutic response, and radiographic progression in patients with early RA after 2 years of therapy with disease-modifying antirheumatic drugs (DMARD).

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MATERIALS AND METHODS

Patients. Consecutive outpatients attending the rheumatology units of the Hospital Clinic, Barcelona, and Hospital Parc Taulí, Sabadell, Spain, and who fulfilled American College of Rheumatology RA criteria[5], and having symptoms < 24 months, were enrolled from 1996 to 2008 and followed for 2 years. Patients previously treated with DMARD or prednisone > 10 mg/day or equivalent were excluded. The study was approved by the Hospital Clinic ethics committee. All patients gave written informed consent.

Study design. In a prospective open-label study, all patients were treated with early introduction of DMARD using sodium aurothiomalate as the first option and methotrexate at an increasing dose of 7.5 to 20 mg weekly in cases of adverse events or poor disease control, and low doses of methylprednisolone (4 mg/day), tapered according to clinical judgment. After 12 months' therapy, aggressive treatment with other DMARD in monotherapy or in combination or biological therapy was introduced according to clinical criteria.

At study entry, these variables were analyzed: demographic characteristics, disease duration, serum RF by nephelometry (normal value < 25 IU/l), ACPA-2 by ELISA (Euro-Diagnostica, Arnhem, The Netherlands; normal < 30 IU/l), anticyclic citrullinated fibrin-filaggrin autoantibodies (CFFCP; in-house test; normal < 0.246 UDO)[6], and the HLA-DRB*1 genotype, determined by direct DNA sequencing. Disease activity was assessed at baseline and every 3 months, recording pain (visual analog scale), the 28-tender joint and swollen joint counts, patient and physician assessment of disease status, the 28-joint Disease Activity Score, the modified Health Assessment Questionnaire, hemoglobin, erythrocyte sedimentation rate, C-reactive protein, and European League Against Rheumatism (EULAR) response criteria.

At inclusion, patients were classified as ever-smokers, past smokers (smoking cessation ≥ 1 year before disease onset) and current smokers at disease onset, and nonsmokers. Pack-year information was collected.

Radiographs of hands and feet, scored by the Larsen-Scott method, were obtained at baseline and 12 and 24 months[7]. An erosion joint count (EJC) was performed[8], defined as the number of joints with cortical erosion out of the 32 joints evaluated. All radiographs were read chronologically by the same observer (RS), who was blinded to the smoking status.

Statistical analysis. Univariate analysis used chi-square or Fisher's exact tests (categorical) and Student t test or Mann-Whitney U test (continuous), as appropriate. Multivariate linear regression analysis was performed. Significance was evaluated at the $\alpha = 0.1$ level and confounding as a change in smoking OR > 15% compared to the full model. No first-order interactions were significant. Intraobserver agreement for the radiographic Larsen score was assessed using kappa statistics on 25 randomly chosen pairs of hand and foot radiographs (kappa = 0.77, 95% CI 0.61–0.93). Analysis was performed using the SPSS v17.0 statistical package.

RESULTS

Of 198 patients initially enrolled, 17 did not complete followup, 10 were lost to followup, 14 had no radiographs at baseline and 24 months, and smoking status was not established in 1 patient. That left 156 patients (83% women) with early RA who were analyzed, of whom 66 (42.3%) were ever-smokers, 47 (30.1%) current smokers, and 23 heavy smokers (> 20 pack/yrs).

Baseline characteristics are shown in Table 1. Current smokers were more frequently men, had an earlier disease onset, and had a significantly higher frequency of the shared epitope (SE) and DRB*04 alleles than nonsmokers. Earlier disease onset was observed in patients with the SE (mean age 51.7 ± 15 vs 58.1 ± 15.2 yrs, respectively; p = 0.04). No differences in the percentage of seropositive disease (RF and ACPA) were found, although RF levels in RF-positive patients were significantly higher in smokers. No differences were observed in other variables.

Clinical disease activity, rates of EULAR clinical response at 12 and 24 months, and the therapy received, including biologicals, were similar in current smokers and nonsmokers (Table 2). Similar results were observed when comparisons were made between ever-smokers and nonsmokers, current heavy smokers and nonsmokers, or only in women (data not shown).

The EJC and Larsen scores were higher in current smokers than in nonsmokers at 12 and 24 months, although the only significant difference was the EJC at 2 years (1.2 ± 1.7 vs 0.7 ± 1.7; p = 0.04). In the multivariate analysis, smoking (current vs nonsmokers), being female, baseline Larsen score, and HLA-DRB*04 were associated with the Larsen score at 24 months. Similar results were obtained when EJC was used as the measure of radiographic damage (Table 3) or when patients receiving biologicals were excluded (data not shown).

DISCUSSION

We analyzed the effect of smoking in patients with early RA 24 months after the introduction of DMARD and found no differences in the clinical progression and therapeutic

Table 1. Baseline characteristics of the early rheumatoid arthritis cohort (current smokers vs nonsmokers). Results are expressed in mean values ± SD or percentages, unless otherwise indicated.

Characteristics	All Patients, n = 156	Current Smokers, n = 47	Nonsmokers, n = 90	p
Women, n (%)	130 (83.3)	30 (63.8)	86 (95.6)	< 0.001
Age, yrs	54.4 ± 14.9	48.3 ± 13.2	57.3 ± 15.1	0.001
Disease duration, mo	9.7 ± 6.6	8.4 ± 5.1	10.3 ± 6.8	0.088
VAS pain, mm	49 ± 23.3	50.6 ± 22.9	49.8 ± 24.1	0.864
Patient global assessment, mm	58.4 ± 15.9	59.1 ± 18.5	58.2 ± 14	0.755
Physician global assessment, mm	56 ± 14	59.3 ± 14.5	54.4 ± 12.3	0.056
28 Tender joint count	9.9 ± 6	9.5 ± 6.4	10.4 ± 5.7	0.856
28 Swollen joint count	7.6 ± 4.3	7.9 ± 4.5	7.6 ± 4	0.677
DAS28	5.6 ± 0.9	5.6 ± 1	5.7 ± 0.9	0.398
Modified HAQ	0.9 ± 0.6	0.97 ± 0.6	0.9 ± 0.6	0.731
ESR, mm/h	40.7 ± 26.4	36 ± 22.6	40.7 ± 25	0.285
CRP, mg/dl	2.8 ± 3	2.6 ± 2.6	2.8 ± 3.2	0.682
Larsen score	1.9 ± 6.9	1.8 ± 6.3	1.2 ± 2.7	0.447
Erosion joint count	0.4 ± 1.3	0.4 ± 0.9	0.3 ± 0.8	0.400
Larsen score ≥ 1, n (%)	48 (30.8)	14 (29.8)	29 (32.2)	0.771
Erosion joint count ≥ 1, n (%)	29 (18.6)	11 (23.4)	14 (15.6)	0.259
RF-positive, n (%)	119 (76.3)	40 (85.1)	67 (74.4)	0.152
RF-positive, IU/l	233.1 ± 487.2	378.7 ± 782.6	138.3 ± 174.9	0.043
ACPA2-positive, %	112/148 (75.7)	36/43 (83.7)	65/88 (73.9)	0.207
ACPA2-positive, IU/l	767.5 ± 615.8	774.1 ± 616.7	772.9 ± 619.5	0.992
CFFCP1-positive, %	73.9	76.5	75	0.872
CFFCP1-positive, ODU	1.5 ± 1	1.6 ± 1	1.4 ± 1	0.388
SE	72.7	92.1	65.3	0.002
SE homozygosity, %	19.5	29	14.7	0.04
HLA-DRB*04, %	44.6	68.4	32.5	0.004

VAS: visual analog scale; DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies; CFFCP: anticyclic citrullinated fibrin-filaggrin autoantibodies; ODU: optical density units; SE: shared epitope.

Table 2. Progression of clinical disease activity, therapeutic responses, and drug therapy (count smokers vs nonsmokers) at 1 and 2 years of followup. Results are mean values ± SD or percentages unless otherwise indicated.

Characteristic	12 Months, n = 137			24 Months, n = 137		
	Nonsmokers, n = 90	Current Smokers, n = 47	p	Nonsmokers, n = 90	Current Smokers, n = 47	p
28 Tender joint count	3.4 ± 5	3 ± 4	0.631	2.5 ± 3.6	2.5 ± 4.1	0.962
28 Swollen joint count	2.2 ± 3.3	1.9 ± 3	0.609	1.9 ± 2.7	1.8 ± 3.8	0.837
Patient global assessment, mm	41.7 ± 17.8	37.8 ± 18	0.233	35.4 ± 19.3	35.6 ± 18.7	0.970
Physician global assessment, mm	35.3 ± 19.5	31.9 ± 18.1	0.335	30.4 ± 18.1	30.5 ± 18.4	0.977
VAS pain, mm	30.8 ± 24.9	25 ± 24.3	0.214	26.3 ± 23.6	27.9 ± 24.1	0.731
ESR, mm/h	28.8 ± 21.1	18.5 ± 12.3	0.003	24.7 ± 17.6	21.7 ± 16.6	0.346
CRP, mg/dl	1.3 ± 1.7	1.1 ± 1.2	0.443	1.2 ± 1.8	1.2 ± 1.8	0.939
Modified HAQ	0.5 ± 0.5	0.4 ± 0.5	0.405	0.5 ± 0.6	0.4 ± 0.5	0.892
DAS28	3.8 ± 1.4	3.5 ± 1.2	0.135	3.5 ± 1.3	3.2 ± 1.2	0.362
Remission (DAS28 < 2.6), n (%)	20/87 (23.0)	11/44 (25.0)	0.798	29/87 (33.3)	15/43 (34.9)	0.860
Low disease activity (DAS28 < 3.2), n (%)	32/87 (36.8)	23/44 (52.3)	0.90	41/87 (47.1)	22/43 (51.2)	0.665
Good EULAR response, n (%)	29/82 (35.4)	23/44 (52.3)	0.079	41/87 (48.2)	22/43 (51.2)	0.223
Moderate EULAR response, n (%)	39/82 (47.6)	12/44 (27.3)	—	28/83 (33.7)	18/43 (41.9)	
No EULAR response, n (%)	14/82 (17.1)	9/44 (20.5)	—	15/83 (18.1)	3/43 (7.0)	
Patients receiving IM gold	68.9	66.0	0.122	42.2	25.5	0.06
Patients receiving methotrexate	40.0	44.7	0.598	44.4	51.1	0.461
Patients receiving TNF antagonists	2.2	4.3	0.607	10.0	6.4	0.545

VAS: visual analog scale; DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; EULAR: European League Against Rheumatism; IM: intramuscular; TNF: tumor necrosis factor.

Table 3. Multivariate regression linear analysis for radiographic progression.

	B	SE	95% CI	p
Larsen-Scott score at 2 years				
Larsen score at baseline	0.881	0.116	0.65, 1.11	0.000
Smoking (past vs nonsmoker)	0.486	2.529	–4.52, 5.49	0.848
Smoking (current vs nonsmoker)	4.274	1.910	0.49, 8.05	0.027
Women	7.142	2.217	2.75, 11.53	0.02
HLA-DRB*04+	5.097	1.624	1.88, 8.31	0.002
EJC score at 2 yrs				
Larsen score at baseline	0.821	0.077	0.67, 0.97	0.000
Smoking (past vs nonsmoker)	–0.065	0.372	–0.8, 0.67	0.861
Smoking (current vs nonsmoker)	0.603	0.282	0.05, 1.16	0.034
Women	0.792	0.327	0.14, 1.44	0.017
HLA-DRB*04+	0.632	0.239	0.16, 1.11	0.009

EJC: erosion joint count; B: regression coefficient.

response between smokers and nonsmokers. However, there were differences in clinical disease presentation and radiographic damage. Disease onset was earlier in smokers, as found by other studies[3]. Earlier disease onset has also been observed in carriers of the SE and DRB*04, which are closely associated with smoking in this and other studies[9], making it difficult to ascertain whether it is associated with smoking, the genetic background, or both. However, the percentage of patients with positive autoantibodies did not differ between smokers and nonsmokers, and only serum RF levels were higher in smokers. We cannot explain this finding, especially as the link between smoking and RA seems to be confined to patients with seropositive disease, having a positive interaction with the SE genotype[10]. However, some prospective studies in whites did not find more seropositive disease in smokers[11].

Disease evolution at 24 months did not differ significantly between current smokers and nonsmokers. Some studies have observed a better clinical course in smokers while others found smoking was associated with greater disease activity or poor therapeutic response to DMARD, including methotrexate and biologicals[2,12].

We found greater radiographic progression in current smokers versus nonsmokers, but it is unclear whether this is attributable to smoking or to confounding factors such as the SE of DRB*04, a known prognostic factor of radiographic damage[8]. However, the multivariate analysis showed current smoking was independently associated with radiographic

damage after 24 months. In prospective studies in early RA[3,12,13,14,15], only one[12] found that active smoking was an independent risk factor for radiographic damage, while in another study heavy smoking was associated with slower progression[11]. Differences in RA populations, methodological issues, or the measurement of smoking may explain these differences.

The limitations of our study include the sample size and the length of followup, which may be insufficient to confirm similar disease courses between smokers and nonsmokers. The effect of the amount of smoking was difficult to ascertain, because of the very small number of current, heavy smokers.

In patients with early RA, smoking was associated with an earlier disease onset and a closer association with the SE and HLA-DRB*04. Disease activity and clinical response after 2 years of DMARD were similar in smokers and nonsmokers. Radiological progression was greater in smokers and was independent of other prognostic factors. However, the effect of smoking on radiographic damage in early RA seems to be mild.

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