Absent "Window of Opportunity" in Smokers with Short Disease Duration. Data from BARFOT, a Multicenter Study of Early Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To study the effect of disease duration and smoking on outcome in early rheumatoid arthritis (RA).

Methods. Between 1996 and 2004, 1587 patients were included in the BARFOT early RA (disease duration ≤ 1 year) study in Sweden. European League Against Rheumatism (EULAR) response, Health Assessment Questionnaire (HAQ), rheumatoid factor (RF), and antibodies to cyclic citrullinated peptide (anti-CCP) were recorded at study start and at 3, 6, and 12 months.

Results. In total, 180 RA patients (11%) had disease duration ≤ 12 weeks. These patients achieved good EULAR response significantly more often at 3 and 12 months than patients with a longer disease duration despite having more aggressive disease [EULAR good response was achieved by 35% and 35% at 3 and 12 months, respectively, among the patients with disease duration ≤ 12 weeks, by 35% and 41% of patients with disease duration of 13–24 weeks, and by 28% and 33% of patients with disease duration of 25–52 weeks ($p = 0.02$ for 3 months; $p = 0.02$ for 12 months)]. There was a significant correlation between improvement in Disease Activity Score-28 (DAS28), its individual variables, and Health Assessment Questionnaire (HAQ) and disease duration up to 12 months after study start. For smokers, no such trend was seen.

Conclusion. Up to 12 months after inclusion in the study, there was a significant correlation between improvement in DAS28, its individual components, and HAQ and disease duration, with patients who had a shorter disease duration improving most. Smokers had poorer EULAR response and showed no improvement with regard to disease duration. (J Rheumatol First Release Aug 1 2011; doi:10.3899/jrheum.100991)

Key Indexing Terms:
EARLY RHEUMATOID ARTHRITIS SMOKING EPIDEMIOLOGY

During the past decade, therapy for rheumatoid arthritis (RA) has progressed to early, aggressive treatment with remission as the favored outcome. Studies have shown that strategies with early treatment with more active disease-modifying antirheumatic drugs (DMARD), glucocorticoids, and structured patient followup aimed at tight control of inflammation can improve results[1,2,3,4,5,6,7,8]. Early RA is a pathologically distinct entity, resulting in a transient "window of opportunity" when antirheumatic treatment has been proven to be more effective and can in some cases result in complete remission, even enabling withdrawal of treatment[1,2,8,9,10,11,12,13,14].

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Supported by grants from the Swedish Rheumatism Association, the Research Department of the County Council of Halland, the Gothenburg District Rheumatology Foundation, The Swedish Society of Medicine, and the Crafoord Foundation. Dr. Söderlin has received speaking fees from Abbott and MSD for educational events.

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Accepted for publication May 11, 2011.

Recently, smoking has been identified as a risk factor for development of RA, interacting with antibodies to cyclic citrullinated peptide (anti-CCP) and the genetic background[15,16], and also for having more severe RA, including extraarticular manifestations[17,18,19,20,21,22,23,24,25,26,27,28,29].

We set out to study very early RA (disease duration ≤ 12 weeks) and to investigate the effect of disease duration and smoking on European League Against Rheumatism (EULAR) outcome measures[30] at 1 year of followup, for patients in a large longitudinal observational study of early RA in Sweden (the BARFOT study). A secondary aim was to study the improvement in Disease Activity Score in 28 joints (DAS28; www.dasscore.nl), its individual variables, and the Health Assessment Questionnaire (HAQ)[31,32] stratified according to disease duration in months, disease activity at baseline, and smoking. Our hypothesis was that patients with RA with disease duration ≤ 12 weeks would have better EULAR outcomes. We also hypothesized that even with a very short duration of disease, patients who smoked would have poorer outcome.

MATERIALS AND METHODS

During the years 1996-2004, 1587 patients ≥ 18 years of age were enrolled in the BARFOT study, a multicenter longitudinal observational study of patients with early RA in southern Sweden[3,33,34,35]. All patients had disease duration

≤ 1 year and all fulfilled the 1987 American College of Rheumatology (ACR) RA classification criteria[36]. Patients with disease duration < 6 weeks were excluded from our study because they did not fulfill the 1987 ACR criteria. Disease duration was evaluated from the start of the RA symptoms. The number of swollen joints (28-joint count), number of tender joints (28-joint count), C-reactive protein level (CRP), erythrocyte sedimentation rate (ESR), the Swedish version of the HAQ[31,32], and visual analog scales (VAS) for pain and general health were measured at study start and at 3, 6, and 12 months and the Disease Activity Score 28-joint count was calculated[30]. The DAS28 is a composite score ranging from 0 (no disease activity) to 10 (maximum disease activity), assessing the number of swollen and tender joints (of 28), ESR, and the patient's global assessment (VAS scale). The patients were classified into 3 EULAR response groups: no response, moderate response, or good response. A good EULAR responder had to demonstrate improvement of at least 1.2 units in DAS28 and achieve an absolute score < 3.2 in DAS28. A nonresponder should show an improvement of < 0.6 or > 0.6 and ≤ 1.2, and have a final DAS28 > 5.1. Moderate EULAR responses fall between these measures. Remission is defined as DAS28 < 2.6, mild disease activity as DAS28 2.61–3.2, moderate disease activity as DAS28 3.21–5.1, and high disease activity as DAS28 > 5.1. The HAQ is a self-completed instrument assessing activities of daily living and function, the score ranging from 0 (no impairment) to 3 (severe impairment)[32]. The Swedish version of the HAQ was used in this study[31]. Changes from baseline to 12 months in HAQ and DAS28 and its individual components were stratified according to disease duration and smoking. Treatment with DMARD and glucocorticoids was recorded at study start and at each followup point. The choice of DMARD treatment in the BARFOT study was left to the discretion of the rheumatologist. Smoking status (never smoker, previous smoker, current smoker) was assessed at inclusion to the study. Pack-year data were not available in this study.

All patients gave their written informed consent and the ethics committee of Lund University approved the study.

Rheumatoid factor and antibodies to CCP. RF was analyzed using the current laboratory methods in each participating hospital. Serum antibodies to CCP were analyzed using the Immunoscan-RA ELISA CCP2 test (Euro-Diagnostica, Malmö, Sweden), performed according to the instructions of the manufacturer. All samples yielding values above the standard curve were diluted further to obtain definite values for all individuals investigated. A titer > 25 units/ml was regarded as positive for anti-CCP.

Statistics. Statistical analyses were performed using PASW 18.0 software. All significance tests were 2-tailed and conducted at the 0.05 significance level. To test for differences between groups, the independent t-test was used for continuous variables and the chi-square test for proportions. Spearman's correlation test was used to assess the relation between 2 continuous variables. Analysis of variance (ANOVA) was used to study the effects of disease duration and smoking on baseline demographics and disease activity. The separate-slopes model (interaction) was used in a post hoc analysis to assess change in the slope of change from baseline to 12 months in DAS28 and HAQ in relation to smoking and disease duration. We performed a multiple logistic regression analysis to determine whether disease duration was a prognostic factor using the EULAR good and/or moderate outcome at 3, 6, and 12 months of followup. The following variables were introduced into the regression model: baseline age, sex, disease duration (months), smoking status, RF, HAQ, DMARD at study start (yes/no), glucocorticoid treatment (yes/no), and DAS28.

RESULTS

In total, 1587 patients had disease duration > 6 weeks and ≤ 12 months. The demographic data and disease activity at inclusion in the BARFOT study are summarized in Table 1. The mean age was 58 years and 68% of subjects were women. The mean time from onset of symptoms to inclusion in the BARFOT study was 5.8 months. Patients with disease duration ≤ 12 weeks had higher disease activity at the start of the study. They also had higher HAQ scores, but were less often RF-positive.

There were complete data at all followup times (3, 6, and 12 months) for 1251 patients (79%). A total of 336 (21%) patients did not have complete data at all followup times. These latter patients did not differ in disease activity from the patients with complete data at baseline except for having lower HAQ (0.94 vs 1.06; p = 0.02). There were no differences in disease duration, sex, RF status, anti-CCP status, or smoking at inclusion between the patients that had complete data and patients with incomplete data. Patients with incomplete data received less DMARD at inclusion (68% vs 83%; p = 0.0001) but there were no differences in the use of glucocorticoids at inclusion. We also assessed attrition and the use of DMARD at inclusion, stratified according to smoking status. Of never-smokers not having complete data, 64% received DMARD at inclusion, previous smokers 66%, and current smokers 76%.

Treatment with DMARD and glucocorticoids stratified by disease duration. There were no statistically significant differences in the percentage of patients treated with DMARD at inclusion or at 3 and 6 months stratified for disease duration. At 12 months, fewer patients with shorter disease duration were treated with DMARD (76%, 84%, 79% for disease duration ≤ 12 weeks, 13–24 weeks, and > 24 weeks, respectively; p = 0.04). There were no differences in methotrexate (MTX) treatment at inclusion, stratified according to disease duration (Table 1). Patients with longer disease duration had received glucocorticoids less often at inclusion (Table 1). There were also statistically significant differences in the use of glucocorticoids at the 6-month followup, patients with a longer disease duration receiving less glucocorticoid (37% of patients with disease duration ≤ 12 weeks were receiving glucocorticoids, compared to 37% of patients with disease duration of 13–24 weeks and 31% of patients with disease duration of 25–52 weeks at 6 months; p = 0.04). The same was true for glucocorticoid treatment at 12 months [38%, 35%, and 28% (p = 0.005) for disease duration ≤ 12 weeks, 13–24 weeks, and > 24 weeks, respectively].

Almost the entire patient cohort was treated with DMARD (96%), predominantly MTX and sulfasalazine. A total of 6 patients received biologic therapy at inclusion and 65 (4%) patients received biologics at 12 months.

Demographics and treatment in smokers. Compared to previous smokers and never-smokers, the patients who smoked at inclusion into the study were significantly younger [mean age of smokers was 56 years (SD 13), previous smokers 60 years (SD 13), and never-smokers 57 years (SD 17); p = 0.0001] and smokers significantly more often were RF-positive (70% of smokers, 61% of previous smokers, and 57% of never-smokers were RF-positive; p = 0.0001) and anti-CCP-positive (66% of smokers, 63% of previous smokers, 53% of never-smokers; p = 0.02). There were no significant differences in

Table 1. Demographics and disease activity at inclusion in the BARFOT study. Values are mean (SD) unless stated otherwise.

Characteristic	All Patients, n = 1587	Disease Duration > 6 wks ≤ 12 wks (n = 180)	Disease Duration 13–24 wks (n = 604)	Disease Duration 25–52 wks (n = 803)	p*
Age at inclusion, yrs	58 (15)	60 (15)	60 (15)	56 (16)	0.0001
Disease duration, mo	5.8 (2.8)	1.8 (0.4)	3.9 (0.8)	8.0 (1.9)	0.0001
Disease duration, wks	27 (12)	9.8 (1.5)	19 (3.4)	36 (7.9)	0.0001
Percentage women	68	63	66	70	0.16
RF, %	61	57	58	65	0.01
Anti-CCP (%)	336/567 (59)	43/69 (62)	118/189 (62)	177/309 (57)	0.57
ESR, mm	40 (25)	47 (27)	38 (25)	34 (25)	0.0001
CRP, mg/l	34 (38)	47 (50)	34 (38)	30 (33)	0.0001
Tender joints 28	8.2 (6.3)	9.4 (6.9)	8.5 (6.4)	7.8 (6.0)	0.002
Swollen joints 28	11 (5.7)	12.0 (5.9)	10.7 (5.7)	9.9 (5.5)	0.0001
VAS pain, mm	47 (24)	53 (25)	47 (24)	46 (23)	0.008
VAS global, mm	46 (25)	50 (27)	46 (25)	45 (25)	0.07
HAQ	1.04 (0.66)	1.32 (0.75)	1.06 (0.66)	0.95 (0.62)	0.0001
DAS28	5.3 (1.2)	5.7 (1.2)	5.4 (1.2)	5.1 (1.2)	0.0001
Methotrexate at inclusion, %	47	48	50	44	0.12
Glucocorticoids at inclusion, %	33	36	36	30	0.046
DMARD at inclusion, %	80	83	80	80	0.59
Current smokers at inclusion, %	24	26	23	24	0.29
Previous smokers at inclusion, %	32	31	35	30	0.29

* Between the 3 categories of disease duration. RF: rheumatoid factor; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; VAS: visual analog scale; HAQ: Health Assessment Questionnaire; DMARD: disease-modifying antirheumatic drug; DAS28: Disease Activity Score (28 joints).

MTX treatment at inclusion, stratified according to smoking (48% of current smokers, 46% of previous smokers, 46% of never-smokers received MTX at inclusion; p = 0.76). Significantly more smokers received treatment with DMARD at inclusion (85% of smokers as compared to 80% of previous smokers and 77% of never-smokers; p = 0.009). However, there were no differences in the proportion of patients receiving DMARD or MTX treatment stratified according to smoking later on (at 3 months p = 0.22, 6 months p = 0.48, and 12 months p = 0.68). There were no significant differences in glucocorticoid treatment at inclusion or at 3, 6, and 12 months stratified according to smoking (data not shown). Smoking had no significant influence on disease activity at inclusion, as measured by DAS28 (p = 0.85).

Disease duration and disease activity measured by the DAS28 and EULAR response. There were significant differences in the frequency of remission between the different smoking classes at 3 months (never-smokers 26%, previous smokers 24%, current smokers 18%; p = 0.03), but not at inclusion (p = 0.91), at 6 months (p = 0.08), or at 12 months (p = 0.07).

There was a significant correlation between shorter disease duration at inclusion and EULAR response (i.e., a good and/or moderate EULAR response) at 12 months of followup (Table 2). We also looked at the absolute values in the DAS28: mild disease activity DAS28 = 2.61–3.2, moderate 3.21–5.1, severe > 5.1, and DAS remission < 2.6, stratified according to disease duration and disease activity at baseline. There were no statistically significant differences in remission, mild disease activity, moderate disease activity, or high disease activity at 3, 6, and 12 months, according to disease duration (data not shown). Stratification of the data according to whether there was no activity, mild, moderate, or high disease activity at baseline and according to disease duration (≤ 12 weeks, 13–24 weeks, or 25–52 weeks) showed that there were no statistically significant differences in EULAR response (i.e., good and/or moderate) at any followup time (data not shown).

EULAR response according to disease duration and smoking. The effects of smoking on EULAR response (good and/or moderate) stratified according to disease duration are shown in Table 3. Briefly, smokers constantly achieved EULAR response less often than never-smokers and previous smokers; the results reached statistical significance at 3 and 6 months of followup for patients with disease duration ≤ 12 weeks and at 12 months for patients with disease duration of 13–24 weeks.

Change in DAS28 from baseline to 12 months, according to disease duration and smoking. There was a significant correlation between change from baseline to 12 months in DAS28 and disease duration, in that patients with shorter disease duration improved most (r_s = 0.167, p = 0.0001; Figure 1). Further, this improvement showed a trend up to 12 months of disease duration in never-smokers (r_s = 0.223, p = 0.0001) and previous smokers (r_s = 0.201, p = 0.0001), but not in current smokers at baseline (r_s = 0.034, p = 0.54; Figure 2). Since the slope of change from baseline to 12 months appeared to level off at 9 months after onset of disease, a post hoc analysis with a separate-slopes model (interaction) was carried out to investigate this phenomenon further, with the cutoff point at 9 months. The post hoc analysis showed no significant change

Table 2. Percentage of patients who had a EULAR response (i.e., a good and/or moderate EULAR response) at 3, 6, and 12 months of followup, stratified according to disease duration. P values are within the groups for EULAR response at 3, 6, and 12 months, each group compared individually. Significance level is $p < 0.05$.

	Disease Duration at Inclusion into the BARFOT Study			
	> 6 and ≤ 12 weeks, n = 180	13–24 weeks, n = 604	25–52 weeks, n = 803	p
3 months, n = 1398	75	72	67	0.06
6 months, n = 1323	72	70	66	0.17
12 months, n = 1367	81	82	76	0.03

Table 3. EULAR response (good and/or moderate) at 12 months, stratified according to smoking status and disease duration. P values are within the smoking categories, stratified according to disease duration, each group being compared individually. The significance level is $p < 0.05$.

Disease Duration	Patients with EULAR Response at 3 mo, %				Patients with EULAR Response at 6 mo, %				Patients with EULAR Response at 12 mo, %			
	Smokers	Previous Smokers	Never-Smokers	p	Smokers	Previous Smokers	Never-Smokers	p	Smokers	Previous Smokers	Never-Smokers	p
≤ 12 wks, n = 180	60	80	80	0.03	54	79	78	0.01	78	81	84	0.72
13–24 wks, n = 604	64	73	75	0.09	62	71	74	0.07	72	85	84	0.01
25–52 wks, n = 803	62	66	70	0.18	62	64	69	0.22	71	77	77	0.25

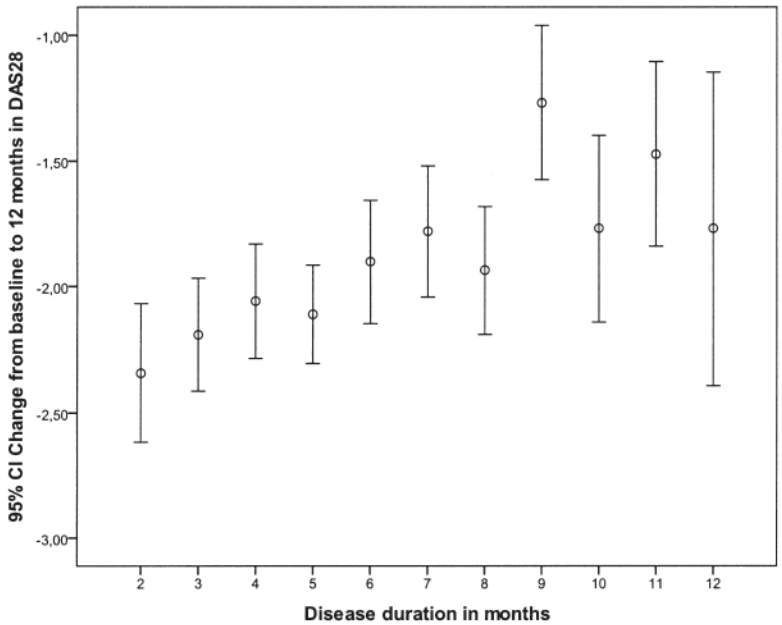

Figure 1. 95% CI for mean change in DAS28 from baseline to 12 months of followup according to disease duration in months.

in the slope of improvement in DAS28 either before or after 9 months ($p = 0.89$). The number of patients in the different categories for disease duration month for month ranged from 23 (at 12 months' disease duration) to 224 (at 5 months' disease duration). For the different smoking categories, the numbers of patients in the different disease durations in never-smokers ranged from 13 (at 12 months' disease duration) to 101 patients (at 5 months), previous smokers 6–76 patients, and current smokers 4–52 patients.

We analyzed the changes from baseline to 12 months in the individual variables of the DAS28, stratified according to smoking status and disease duration. Smokers had no significant improvement in change from baseline to 12 months in all of the individual components of the DAS28 (swollen joints, $r_s = 0.052$, $p = 0.33$; tender joints, $r_s = 0.034$, $p = 0.53$; ESR, $r_s = 0.066$, $p = 0.22$; and VAS global, $r_s = –0.035$, $p = 0.52$). Also, previous smokers had no significant improvement in change from baseline to 12 months in tender joints and VAS

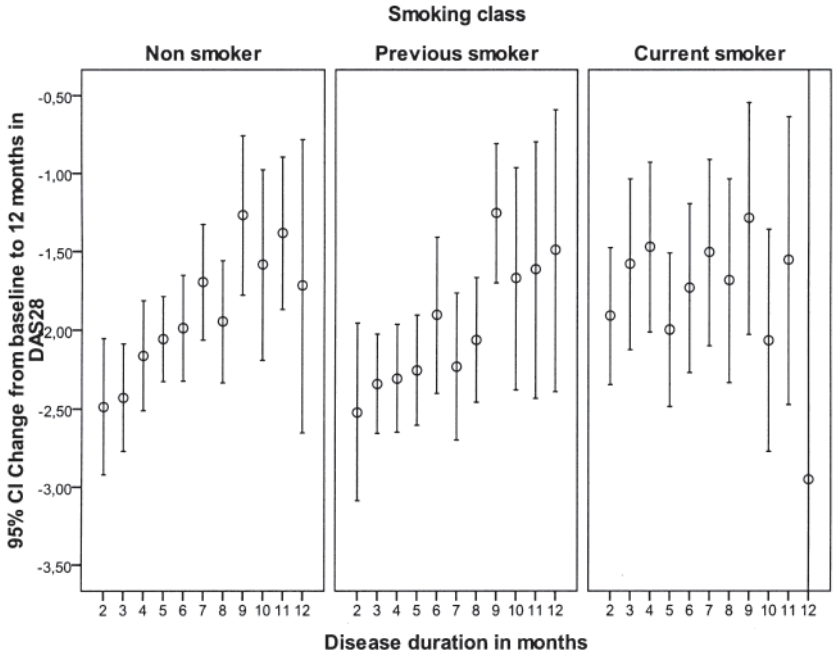

Figure 2. 95% CI for mean change in DAS28 from baseline to 12 months according to disease duration in months and smoking status.

global when plotted against disease duration (tender joints, $r_s = 0.085$, $p = 0.07$; VAS global, $r_s = 0.089$, $p = 0.05$). For never-smokers, the changes from baseline to 12 months plotted against disease duration were significant for all the individual variables of the DAS28 (swollen joints, $r_s = 0.192$, $p = 0.001$; tender joints, $r_s = 0.179$, $p = 0.0001$; ESR, $r_s = 0.164$, $p = 0.0001$; and VAS global, $r_s = 0.155$, $p = 0.0001$).

Change in HAQ from baseline to 12 months, according to disease duration and smoking. There was a significant correlation between disease duration and change from baseline to 12 months in HAQ ($r_s = 0.12$, $p = 0.0001$; Figure 3). There was also a significant correlation between disease duration and difference from baseline in HAQ at 12 months for never-smokers and previous smokers, but not for current

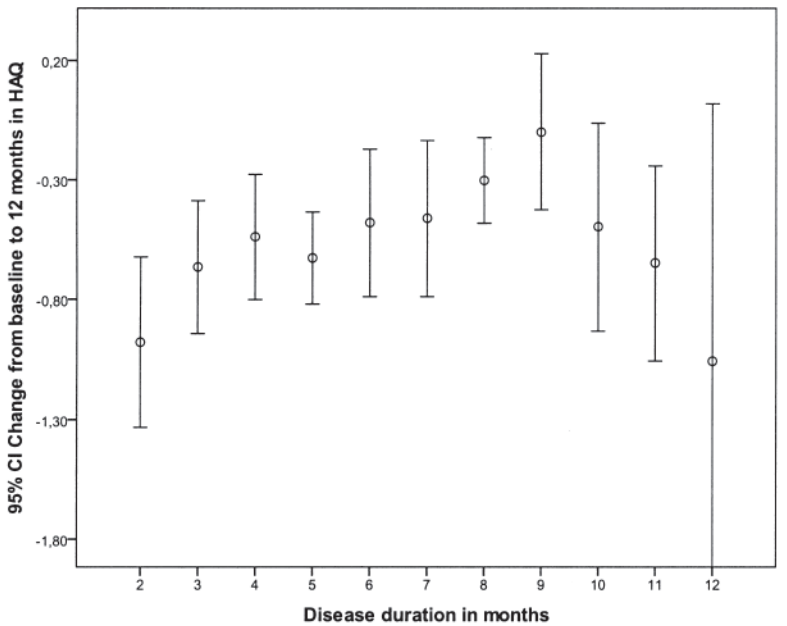

Figure 3. 95% CI for mean change in HAQ from baseline to 12 months according to disease duration in months.

smokers (never-smokers, r_s = 0.160, p = 0.0001; previous smokers, r_s = 0.134, p = 0.004; and current smokers, r_s = 0.027, p = 0.62; Figure 4). The separate-slopes model did not show any significant change in the slope of improvement in HAQ before or after 9 months (p = 0.10).

Change in DAS28 from baseline to 12 months, according to disease duration, smoking, and disease activity at inclusion. The change in DAS28 from baseline to 12 months was plotted against disease duration for the 919 patients (58%) who had high disease activity at inclusion (DAS28 score > 5.1). In these patients, for never-smokers and previous smokers there was a significant correlation between change in DAS28 from baseline to 12 months and disease duration in months (never-smokers, r_s = 0.160, p = 0.002; previous smokers, r_s = 0.179, p = 0.003), but no such correlation was seen for current smokers (r_s = –0.006, p = 0.94). For smokers with high disease activity, there was no correlation between change from baseline to 12 months and disease duration in the individual variables of the DAS28, VAS pain, or HAQ (data not shown). When we looked separately at patients with moderate disease activity at baseline [DAS28 score 3.2–5.1, n = 536 (34%)], for never-smokers there was a significant correlation between disease duration and change in DAS28 from baseline to 12 months (r_s = 0.230, p = 0.0001), but for previous smokers there was no such correlation (r_s = 0.139, p = 0.09) and this applied to current smokers also (r_s = –0.027, p = 0.77). Smokers with moderate disease activity did not show any correlation between disease duration and change from baseline to 12 months in any of the individual variables in the DAS28, VAS pain, or HAQ (data not shown).

Multiple logistic regression analysis. A multiple logistic regression analysis was performed to determine whether disease duration was an independent prognostic factor for good and/or moderate EULAR response at 3, 6, and 12 months. Disease duration in months emerged as a poor prognostic factor for EULAR response at 12 months (OR 0.94, 95% CI 0.90–0.98, p = 0.006) but not at 3 months (OR 0.96, 95% CI 0.92–1.00, p = 0.07) or 6 months (OR 0.97, 95% CI 0.93–1.02, p = 0.20). Current smoking at inclusion in the study was an independent negative prognostic factor for EULAR response up to the 12-month followup (Table 4). We analyzed the 316 (20%) patients who were not included in the logistic regression analysis at 12 months compared to the 1271 (80%) patients who were included in the model. The patients not included in the model were older (mean 60 vs 58 years; p = 0.003), had higher VAS global scores (mean 49 mm vs 45 mm; p = 0.003), and had higher ESR (mean 40 mm vs 36 mm; p = 0.02) at inclusion, but they did not otherwise differ in disease activity, serology, or demographics. The patients not in the regression model at 12 months received DMARD at inclusion less often (73% vs 82%; p = 0.0001), but they did not differ in glucocorticoid treatment at inclusion.

DISCUSSION

To our knowledge this is the first study to report disease improvement in DAS28, in its individual variables, and in HAQ, plotted month by month, during the first year of followup in early RA. The improvements had a significant association with disease duration, patients with shorter disease duration improving most despite having higher disease activ-

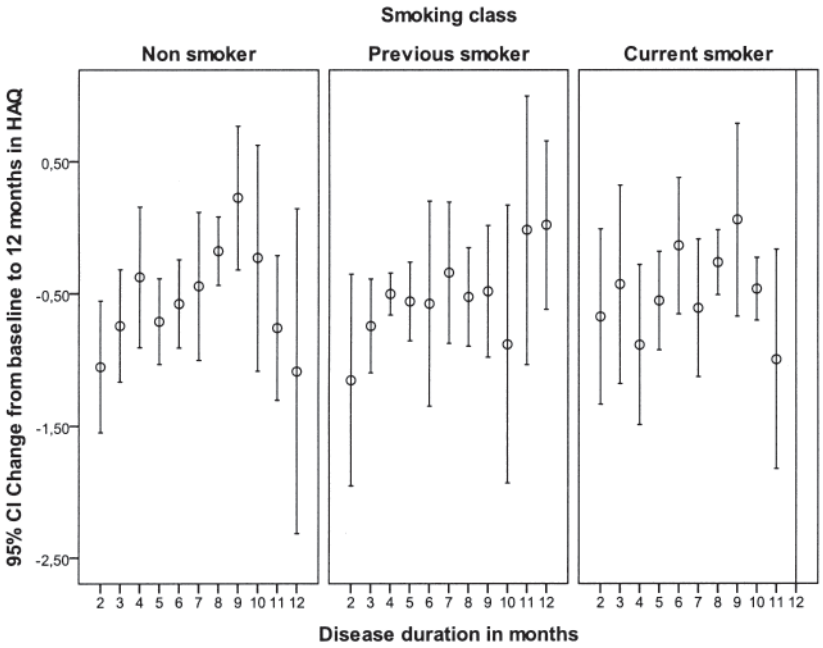

Figure 4. 95% CI for mean change in HAQ from baseline to 12 months according to disease duration in months and smoking status at baseline.

Table 4. Multivariate logistic regression analysis using good and/or moderate EULAR response as outcome at 3, 6, and 12 months.

Variable (at inclusion)	3 Months, N = 1301 OR (95% CI)	p	6 Months, N = 1232 OR (95% CI)	p	12 Months, N = 1271 OR (95% CI)	p
Age (decades)	1.0 (0.92–1.09)	0.95	1.00 (0.91–1.09)	0.92	0.94 (0.87–1.02)	0.12
Female	0.78 (0.59–1.03)	0.07	0.75 (0.56–0.99)	0.04	0.51 (0.39–0.66)	0.0001
Previous smoker	0.76 (0.56–1.02)	0.07	0.73 (0.54–0.99)	0.04	0.96 (0.73–1.26)	0.75
Current smoker	0.56 (0.41–0.77)	0.0001	0.56 (0.41–0.77)	0.0001	0.69 (0.51–0.95)	0.02
RF	0.84 (0.65–1.09)	0.20	0.84 (0.65–1.10)	0.22	0.82 (0.65–1.05)	0.12
HAQ	0.76 (0.61–0.96)	0.02	0.77 (0.61–0.97)	0.02	0.85 (0.69–1.06)	0.15
DMARD treatment	1.83 (1.34–2.51)	0.0001	1.90 (1.37–2.63)	0.0001	1.46 (1.06–2.01)	0.02
Disease duration, mo	0.96 (0.92–1.00)	0.07	0.97 (0.93–1.02)	0.20	0.94 (0.90–0.98)	0.006
Glucocorticoid treatment	1.36 (1.03–1.78)	0.03	1.40 (1.07–1.85)	0.02	0.93 (0.72–0.19)	0.55
DAS28	1.56 (1.38–1.77)	0.0001	1.60 (1.41–1.83)	0.0001	0.82 (0.73–0.92)	0.001

RF: rheumatoid factor; HAQ: Health Assessment Questionnaire; DMARD: disease-modifying antirheumatic drug; DAS28: Disease Activity Score (28 joints).

ity. Our study mirrors a "real-life" setting where such severely ill patients were referred from primary healthcare for a fast rheumatological consultation. Early treatment improves outcome in RA, as reported in several studies and one meta-analysis[8,12,37]. Our results give further support to the "window of opportunity" theory, even though disease duration, patient allocation, and treatment could not be randomized in this longitudinal observational study. Further, disease duration was found to be an independent predictor of poor EULAR response at the 12-month followup in the multivariate logistic regression analysis. There were no significant differences in DMARD treatment when stratified according to disease duration at inclusion, but patients with a shorter disease duration received less DMARD at 12 months, a fact difficult to explain. Patients with longer disease duration received less glucocorticoid at inclusion and at 6 and 12 months. The higher prevalence of glucocorticoids in patients with shorter disease duration could mirror the need to treat high disease activity in this study.

Smokers did not reveal any "window of opportunity," meaning that there was no correlation between disease duration and improvement in HAQ, DAS28, or any of its individual components from baseline to 12 months. Also, previous smokers showed no improvement in tender joints and VAS global scores when improvement from baseline to 12 months was plotted against disease duration. These data on the "closed window" in smokers may be due to poorer response to DMARD in smokers. However, to our knowledge no previous study has reported a missing correlation of improvement in disease activity and disease duration in smokers in the way we have shown. Our previous study from this same material showed that smoking at baseline was an independent predictive factor of poor response to therapy even adjusted for RF and anti-CCP status[19], and this finding has been confirmed in 2 other Swedish studies[20,21]. Poorer response to biologic therapies in smokers has also been reported in 3 studies from the UK[27,28,29]. We previously reported from the same material that smoking is associated with RF positivity and anti-CCP positivity[19] as reported by others[22,23,24,25,26], and these factors are known to be associated with a poorer outcome. However, we had anti-CCP data for only a minority of patients and we had no genetic data, so we could not adjust for these confounders, although these factors did not influence the results in another Swedish study[20]. Studies have shown that smokers have higher CRP irrespective of whether they have RA or not[38].

It is not known why smoking has a negative effect on outcome in RA. One reason may be an interaction between smoking and DMARD. It has been reported that smokers may need more DMARD to control higher disease activity and/or pain, and they may even have a higher clearance of DMARD[26]. Smokers have been shown to have lower levels of MTX polyglutamates, the active form of the drug[39]. However, there is no absolute correlation of the levels of MTX polyglutamates with effect[40]. Smoking may continue to influence or interact with the mechanisms behind disease onset even after the onset of RA.

We previously reported from this same material that current smokers (compared to previous smokers) were younger at inclusion, more often RF-positive, more often women, and more often anti-CCP-positive. However, there were no differences in disease activity as measured by swollen or tender joints, HAQ, DAS28, or glucocorticoid treatment. Current smokers received MTX more often in our earlier study[19]. We have no data on lifestyle factors but will assess this in an upcoming study.

One strength of this study was the substantial amount of well documented material, with a tight and comprehensive followup. Smoking status and RF were known for all patients at inclusion. In future analyses we will study the effect of cessation of smoking on disease activity. This study was planned in 1990 and the inclusion criteria were that the patients should fulfil the 1987 ACR criteria of RA[36]. We are not able to assess the data according to the new ACR/EULAR RA criteria[41]. The 1987 criteria do not perform well in very early RA and thus it may be hypothesized that some patients with early and/or mild RA have been excluded from the present study, presenting a bias. One limitation of the study is also the small number of

patients in the different subgroups when stratifying for disease duration in months and smoking, as indicated by the very wide 95% confidence intervals in some groups of disease duration. Our findings must thus be verified in larger studies. We found that the patients with incomplete data received less baseline DMARD, but smokers with incomplete data received DMARD at baseline somewhat more often, compared to never-smokers and previous smokers. However, we do not think that differential attrition explains our results.

It may be argued that our correlation coefficients of the magnitude of r_s = 0.167 in, for example, the association between disease duration and DAS28 are modest, but our large sample size makes these figures statistically significant. Another possible cause for bias is smokers classifying themselves are never-smokers. However, we have questionnaire data on smoking in a subgroup of patients and have shown the validity of the smoking data to be good[17]. We do not have a good explanation why smokers were treated more actively with DMARD initially as our data show no objective differences in disease activity at inclusion stratified according to smoking. This treatment choice may mirror the rheumatologist's subjective assessment. We chose to use the Spearman's rho to analyze the relationship of the change from baseline to 12 months in DAS28 and HAQ correlated to disease duration in months. The differences in DAS28 and HAQ were normally distributed but we wanted to allow for some deviation from a linear association. Visually the slope of the curves seemed to change at around 9 months of followup, but our post hoc analysis did not show any change. Longitudinal and survival analysis methods could have improved the statistical power and provided a possibility to adjust for confounding factors and attrition in this study. Our analyses imply semi-related samples over time, which presents a limitation to the study.

Patients with RA with very short disease duration (≤ 12 weeks) had better outcomes, measured by EULAR response, than patients with longer disease duration, despite having more aggressive disease. The "window of opportunity" data in our study showed that there was a correlation between the improvement from baseline to 12 months in the DAS28, its individual components, VAS pain, and HAQ up to 12 months of disease duration. Smokers were found to have no "window of opportunity"; for them there was no correlation between disease duration and improvement in DAS28, its individual components, or HAQ, and they improved even less in very early RA. However, due to the small numbers of patients in several of the subanalyses and the very broad confidence intervals our data must be confirmed in larger studies. Further research is also needed to study whether there is a dose effect or a threshold effect of smoking on response to therapy.

ACKNOWLEDGMENT

We thank Jan-Åke Nilsson for invaluable help with the statistical analyses. We are grateful for the cooperation of all the centers that supplied data for the BARFOT study.

APPENDIX

List of study collaborators. Members of the BARFOT Study Group: Sofia Ajeganova, Maria Andersson, Valentina Bala, Kristina Forslind, Ingiäld Hafström, Catharina Keller, Ido Leden, Bengt Lindell, Ingemar Petersson, Christoffer Schaufelberger, Björn Svensson, Annika Teleman, Jan Theander, and Anneli Östenson.

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