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. (First Release Aug 1 2011; J Rheumatol 2011;38:2160–8; doi:10.3899/jrheum.100991)

Key Indexing Terms:
EARLY RHEUMATOID ARTHRITIS
SMOKING
EPIDEMIOLOGY

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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 AbbV and MSD for educational events.

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Accepted for publication May 11, 2011.

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. 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.

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, and also for having more severe RA, including extraarticular manifestations.

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 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.das-score.nl), its individual components, and the Health Assessment Questionnaire (HAQ) 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. All patients had disease duration...
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 signifi-
There were significant differences in remission, mild disease activity duration and disease activity at baseline. There were no statistically significant differences in glucocorticoid treatment at inclusion or disease activity, moderate disease activity, or high disease activity at stratification of the data according to whether there were no statistical-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 statistical-ly 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 more (rs = 0.167, p = 0.0001; Figure 1).

![Image](https://www.jrheum.org)
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.
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, $r_s = 0.179$, $p = 0.001$; 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 2. 95% CI for mean change in DAS28 from baseline to 12 months according to disease duration in months and smoking status.](image1)

![Figure 3. 95% CI for mean change in HAQ from baseline to 12 months according to disease duration in months.](image2)
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.
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-analysis8,12,17. 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 status19, and this finding has been confirmed in 2 other Swedish studies20,21. Poorer response to biologic therapies in smokers has also been reported in 3 studies from the UK27,28,29. We previously reported from the same material that smoking is associated with RF positivity and anti-CCP positivity19 as reported by others22,23,24,25,26, 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 study20. Studies have shown that smokers have higher CRP irrespective of whether they have RA or not38.

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 DMARD26. Smokers have been shown to have lower levels of MTX polyglutamates, the active form of the drug39. However, there is no absolute correlation of the levels of MTX polyglutamates with effect40. 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 study19. 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 RA36. We are not able to assess the data according to the new ACR/EULAR RA criteria41. 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

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

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

RF: rheumatoid factor; HAQ: Health Assessment Questionnaire; DMARD: disease-modifying antirheumatic drug; DAS28: Disease Activity Score (28 joints).
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 $r = 0.167$ 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 as 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. 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 ($\leq 12$ 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 Ajevanova, Maria Andersson, Valentina Bala, Kristina Forslund, Ingjuldf Hafstrom, Catharina Keller, Ido Leden, Bengt Lindell, Ingemar Petersson, Christoffer Schauffelberger, Bjorn Svensson, Annika Teleman, Jan Theander, and Anneli Ostenson.

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