Effects of smoking on the clinical phenotype and response to treatment in rheumatoid arthritis

Smoking is the most studied and widely accepted environmental risk factor for the development of seropositive rheumatoid arthritis, especially in subjects with genetic susceptibility (shared epitope carriers). However, the effect of smoking on aspects of rheumatoid arthritis, such as disease presentation, inflammatory activity, disability and joint damage (radiographic progression), is not clear. Recent data strongly suggest a poor response to methotrexate and TNF antagonists in smokers. We review and analyze the current literature on the relationship between smoking and the clinical phenotype and outcomes of rheumatoid arthritis.

KEYWORDS: ACPA ■ disease activity ■ joint damage ■ response to treatment ■ rheumatoid arthritis ■ smoking

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Rheumatoid arthritis (RA), the most common autoimmune joint disease, with a worldwide prevalence of approximately 0.5–1%, is a chronic, progressive disease that causes disability and reduced life expectancy [1]. The etiology is multifactorial and only partially understood, although genetic and environmental factors interplay in its development. Although a number of environmental factors have been implicated in the etiology of RA, the only well-established environmental risk factor is smoking, which has been associated with an increased risk of RA in various studies [2–6]. However, this increased risk is limited to seropositive RA (rheumatoid factor [RF] and/or anticyclic citrullinated peptide [anti-CCP]-positive RA) and not seronegative RA [5,7]. Studies have also shown that rheumatoid factor positivity in healthy subjects is more frequent among smokers, suggesting that smoking may influence the immune system, inducing an immune response [8,9]. Likewise, an interaction between smoking and genetic susceptibility has been shown. Ever having smoked has been associated with a more than sixfold increased risk of anti-CCP antibody-positive RA in individuals with a single copy of the *HLA-DR SE* gene and a more than 20-fold increased risk in individuals with two copies of these genes [10]. It has been estimated that smoking is responsible for 35% of anticitrullinated protein/peptide antibody-positive (ACPA) cases [11]. In addition, smoking also seems to influence disease expression, response to treatment and outcome, although the published evidence is not conclusive. This review examines the factors mentioned above.

Smoking & clinical phenotype

■ Smoking & clinical phenotype of RA at disease onset

Smoking not only increases the risk of seropositive RA, but can also influence the clinical phenotype or disease expression. RA patients who smoke are more frequently male and significantly younger at disease onset, as shown by various cohort studies [12–16]. In some studies, the age difference may be 5, or even 9, years [12,16], a significant difference in a chronic, progressive and disabling disease such as RA. Smoking seems to have no effect on disease severity at disease onset. Most, but not all, studies analyzing early RA cohorts found no differences in disease activity, number of tender and swollen joints, levels of C-reactive proteitn (CRP) and erythrocyte sedimentation rate (ESR), disability or radiological joint damage at disease onset [14,16,17]. However, one study found that smokers had more severe disease at onset than nonsmokers, in addition to significantly higher disease activity, acute phase reactants and joint damage [13]. However, in this study, more than 85% of current smokers were heavy smokers, which could explain the differences found with other studies, as the dose-related effect of smoking has been noted in other aspects of RA influenced by smoking, such as the probability of developing RA or the response to treatment. Another study found that smokers rated their pain as significantly worse than nonsmokers at baseline and also had a significantly more frequent need for disease-modifying antirheumatic drug (DMARD) combination therapy and NSAIDs, but there were no differences

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in disease activity and functional capacity at baseline [12]. Likewise, a study of 100 early RA patients who smoked found they had greater swollen and tender joint count scores at disease onset than former and never smokers with early RA, although no differences were found in CRP levels [18].

Thus, smoking appears to be an important risk factor for the development of RA at a younger age, but does not seem to be associated with more active or disabling disease at presentation.

Smoking & disease course in established RA

Smoking at disease onset does not seem to determine a more active disease, but may be associated with more severe disease thereafter in terms of disease activity and also extra-articular involvement such as nodules, lung disease and vasculitis [12,14,19–24].

The analysis of RA disease activity during follow-up in smokers and nonsmokers has produced inconsistent results, with some studies reporting more active disease with higher acute phase reactants and less probability of a good European League Against Rheumatism (EULAR) response after DMARD therapy in smokers [12,13,17,18,25], while others found no difference between smokers and nonsmokers after comparing different variables of disease activity after 2 or 3 years of follow-up [15,16]. One study even found that smokers were less likely to have persistent synovitis than nonsmokers [14]. However, studies mainly agree that extra-articular manifestations seem to be more frequent in smokers. A retrospective cohort study of 609 RA patients that investigated trends in the incidence of extra-articular manifestations found that smoking was a main predictor of severe extra-articular RA (together with disability and an older age) at RA diagnosis [26]. Other groups confirmed these results [27], showing that smokers more frequently have rheumatoid nodules [13,14,19,20,22,23] and lung disease [19,22,28]. The results of these studies are shown in **Table 1**.

The effect of smoking cessation on disease activity or outcomes after diagnosis has been studied in two cohorts: a US cohort of longstanding RA patients [29]; and a cohort of recent-onset RA patients [30]. Neither found any benefit of smoking cessation on disease activity. However, these were retrospective studies: patients who stopped smoking may have done so due to other comorbidities, poor health or factors not analyzed. An analysis of the Barfot cohort of patients with early RA found no association between secondhand exposure to smoking and disease activity during a 5 year follow-up period [31].

Smoking & RA outcomes

Smoking & joint damage

The relationship between smoking and erosive disease has been widely studied but remains unclear, with some studies showing detrimental effects [13,19–22] and others finding no effect [14,18,23,32], while one study even suggests that smoking may protect against joint damage [15]. The first published studies observed a clear and significant association between radiographic joint damage and smoking; some even reported a dose-dependent response with cumulative smoking exposure on radiographic damage [22]. However, the majority were cross-sectional analyses of cohorts with established, longstanding RA (disease duration >10 years) [19–22]. These studies also confirmed a higher frequency of RF among smokers, but had limited power to establish the temporal nature of events in a cohort with longstanding disease, limiting the ability to establish causal relationships. Furthermore, these studies did not analyze various factors that could influence disease severity, such as disease activity, disability and joint damage at disease onset, serologic factors such as anti-CCP, genetic factors such as the shared epitope, the treatment received or even socioeconomic factors.

In early RA cohorts, the analysis of the relationship between smoking and joint damage and radiographic progression shows conflicting results in longitudinal and cross-sectional studies [12–18,23,32]. Most studies found no effect of current or past smoking on joint damage at disease onset or radiographic progression after 2 or 3 years of follow-up [18,23]. For example, a multicenter study of 379 early RA patients that investigated the association between anti-CCP and radiological outcome found that anti-CCP were associated with a significantly higher Larsen score at baseline and at study end points. Univariate analysis showed that baseline Larsen score, anti-CCP, RF, ESR, CRP, age, smoking status and sex were significantly associated with radiological joint damage and progression. However, in the multiple regression analyses, baseline Larsen score, anti-CCP and ESR, but not smoking, were significant independent predictors of radiological outcomes [32]. Likewise, another cohort of 894 smokers with recent-onset RA had significantly higher

Table 1. Studies on the effect of smoking on rheumatoid arthritis disease activity, joint damage, disability and extra-articular disease.

Study (year)	Study population (mean disease duration)	Smoking status	Effect of smoking on age at onset of RA disease	Effect of smoking on RA disease activity	Effect of smoking on radiologic joint damage	Effect of smoking on HAQ	Effect of smoking on extra-articular disease	Ref.
Saag *et al.* (1997)	336 RA (14 years)	12% current smokers 40% ex-smokers 48% never smokers		Correlation between TJC and pack-year ($p \leq 0.01$)	More joint damage in smokers, OR: 2.37; 95% CI: 1.23–4.56 for HS	HAQ correlated with pack-years (NS trend)	More risk of rheumatoid nodules in smokers (OR: 1.25; 95% CI: 0.70–2.22)	[19]
Wolfe (2000)	640 RA (14 years)	18% current smokers 28% ex-smokers 54% never smokers Mean: six pack-year		NA	Smoking associated with more radiographic progression	NA	Current and ex-smokers increased risk of rheumatoid nodules (OR: 2.35; 95% CI: 1.60–3.46) and more pulmonary disease	[22]
Masdottir *et al.* (2000)	63 RA women (14 years)	32% current smokers 33% ex-smokers 35% never smokers 49% HS		NA	At disease onset, NA At study time, HS higher radiographic score ($p = 0.02$)	NA	HS higher risk of rheumatoid nodules ($p = 0.01$)	[20]
Mattey *et al.* (2002)	164 RA women (11 years)	30% current smokers 21% ex-smokers 49% never smokers Mean 24.8 pack-year			Larsen score, current smokers 99.3 vs never smokers 83.1 ($p = 0.05$) NA between pack-year and Larsen score	HAQ current smokers 1.71 vs never smokers 1.39 ($p = 0.02$)		[21]
Harrison *et al.* (2001)	368 RA (eRA) 3-year follow-up	26% current smokers 43% ex-smokers 31% never smokers	50 years current smokers vs 54 years never smokers	NA (with a trend towards less activity – SJC – in smokers)	NA	NA	Current smokers OR: 4.07 (95% CI: 1.38–12.0)	[14]
Forslind *et al.* (2004)	379 RA (eRA) 2-year follow-up	60% current/ ex-smokers 40% never smokers			In univariate analysis, smoking status associated with radiographic damage and progression In stepwise logistic regression analysis, NA			[32]

ACR50: Percentage of study participants achieving 50% of the ACR response criteria; CRP: C-reactive protein; DAS28: Disease Activity Score over 28 joint count; eRA: Early rheumatoid arthritis; ESR: Erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; HAQ: Health Assessment Questionnaire; HS: Heavy smoker; NA: No association found; NQ: Tobacco consumption not quantified; NS: Not significant; OR: Odds ratio; RA: Rheumatoid arthritis; RF: Rheumatoid factor; SJC: Swollen joint count; TJC: Tender joint count.

Table 1. Studies on the effect of smoking on rheumatoid arthritis disease activity, joint damage, disability and extra-articular disease (cont.).

Study (year)	Study population (mean disease duration)	Smoking status	Effect of smoking on RA age at disease onset	Effect of smoking on RA disease activity	Effect of smoking on radiologic joint damage	Effect of smoking on HAQ	Effect of smoking on extra-articular disease	Ref.
Papadopoulos *et al.* (2005)	287 RA (eRA) 2-year follow-up	29% current smokers 7% ex-smokers 64% never smokers 85% HS	52 years current smokers vs 56.6 never smokers	At baseline and follow-up current smokers higher disease activity (SJC, TJC, CRP and ESR)	Higher Larsen score in current smokers at baseline and follow-up In regression analysis after adjustment for multiple variables, no independent significant association with smoking status		Higher risk of rheumatoid nodules in current smokers	[13]
Manfredsdottir *et al.* (2006)	100 RA (eRA) 2-year follow-up	34% current smokers 38% ex-smokers 28% never smokers Mean: 25 pack-year	48.8 years current smokers vs 53.4 all cohort	Smokers higher SJC and TJC at onset and follow-up	NA (smoking on radiological progression nor pack-year)			[18]
Finckh *et al.* (2007)	2004 RA (6–7 years) 3-year follow-up	27% current smokers 0% ex-smokers 72% never smokers 10% HS	51 years HS vs 56 years never smokers (at inclusion)	NA	Smokers had less radiographic progression	NA		[15]
Westhoff *et al.* (2008)	896 RA (eRA) 3-year follow-up	27% current smokers 23% ex-smokers 50% never smokers 45% HS	51 years smokers vs 58.6 never smokers ($p = 0.000$)	Current smokers (both RF+ and -) worse outcome (higher SJC, DAS28, CRP)	Radiographic progression associated with current smoking After multivariate logistic regression analysis, no influence of smoking on radiographic outcome	NA		[12]
Mikuls *et al.* (2008)	300 RA (eRA; African–Americans) Cross-section	30% current smokers 22% ex-smokers 48% never smokers 18% HS			NA		Rheumatoid nodules more frequent in smokers (OR: 2.46; 95% CI: 1.13–5.22), dose effect	[23]

ACR50: Percentage of study participants achieving 50% of the ACR response criteria; CRP: C-reactive protein; DAS28: Disease Activity Score over 28 joint count; eRA: Early rheumatoid arthritis; ESR: Erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; HAQ: Health Assessment Questionnaire; HS: Heavy smoker; NA: No association found; NQ: Tobacco consumption not quantified; NS: Not significant; OR: Odds ratio; RA: Rheumatoid arthritis; RF: Rheumatoid factor; SJC: Swollen joint count; TJC: Tender joint count.

Table 1. Studies on the effect of smoking on rheumatoid arthritis disease activity, joint damage, disability and extra-articular disease (cont.).

Study (year)	Study population (mean disease duration)	Smoking status	Effect of smoking on RA age at disease onset	Effect of smoking on RA disease activity	Effect of smoking on radiologic joint damage	Effect of smoking on HAQ	Effect of smoking on extra-articular disease	Ref.
Naranjo *et al.* (2010)	7307 RA (multicenter, 32 countries) Cross-section	20% current smokers 15% ex-smokers 65% never smokers		NA	NA	NA	Rheumatoid nodules more frequent in ever smoked 23 vs 17.5% in never smokers, $p < 0.001$	[27]
Söderlin *et al.* (2011)	1787 RA (eRA) 1-year follow-up	24% current smokers 32% ex-smokers 44% never smokers NQ	56 years current smokers/60 years ex-smokers vs 58 years never smokers	Baseline, NA Follow-up, smokers more active disease (higher DAS28, less proportion of good EULAR response and remission)		NA		[17]
Rojas-Serrano *et al.* (2011)	144 RA (eRA) 6-month follow-up	17% current smokers 83% never smokers/ ex-smoker NQ		Of ACR50 responders 9% current smokers, of ACR50 nonresponders 27% current smokers ($p < 0.008$) OR: 3.58 (95% CI: 1.23–11.22)				[25]
Ruiz-Esquide *et al.* (2011)	156 RA (eRA) 2-year follow-up	30% current smokers 12% ex-smokers 58% never smokers 35% HS	48.3 years current smokers vs 57.3 never smokers ($p = 0.001$)	NA	Baseline, NA At follow-up, smokers more radiographic progression	NA		[16]

ACR50: Percentage of study participants achieving 50% of the ACR response criteria; CRP: C-reactive protein; DAS28: Disease Activity Score over 28 joint count; eRA: Early rheumatoid arthritis; ESR: Erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; HAQ: Health Assessment Questionnaire; HS: Heavy smoker; NA: No association found; NQ: Tobacco consumption not quantified; NS: Not significant; OR: Odds ratio; RA: Rheumatoid arthritis; RF: Rheumatoid factor; SJC: Swollen joint count; TJC: Tender joint count.

radiographic scores at baseline compared with nonsmokers. A rather weak association was found between smoking and joint damage at 3 years of follow-up, but multivariate logistic regression found no influence of smoking on radiographic outcomes [12]. A Greek study of 287 patients with early RA found that smokers had significantly more joint damage at baseline and at last follow-up, with a Larsen score of 32.37 in current smokers and 17.11 in never smokers ($p < 0.001$). Multivariate analysis adjusted for sex, age, educational level and alcohol consumption showed a significant independent association between current smoking and disease activity and baseline Larsen score, but not during follow-up. Regression analysis at the end of the study, after adjustment for age, sex, disease activity, baseline Larsen score and RF found no independent association with smoking status [13]. Other studies found no association between radiographic progression in early RA and smoking [18,23]. However, our group found an association between smoking and radiographic progression in a prospective

study in 156 early RA patients: the Larsen score and the erosion joint count at 12 and 24 months of follow-up was higher in smokers than in nonsmokers [16]. In the multivariate analysis, baseline Larsen score, female sex, *HLA-DRB*04* and current smoking (vs nonsmoker) were independent factors for the Larsen score and erosion joint count at 24 months of follow-up.

Curiously, some studies have found smoking to be a protective factor against joint damage in RA. For example, a Swiss study found an inverse dose–response effect for heavy smokers compared with moderate smokers and nonsmokers on the progression of radiographic damage, added to a significantly slower progression of radiographic erosions in heavy smokers compared with nonsmokers [15]. Harrison *et al.* found a trend toward less radiographic damage in current smokers, although no significant association between smoking and radiographic damage was observed [14].

In summary, the evidence on the effect of smoking on joint damage is mixed. This may be due to differences in study designs: in cross-sectional and retrospective studies, patients may have not have received protocolized treatment, which could have influenced the outcomes; other studies did not analyze prognostic markers of radiographic progression such as the shared epitope or anti-CCP. Lastly, most longitudinal studies had a follow-up of 2 to 3 years, which may not be enough to evaluate the effect of smoking on radiographic damage. Table 1 summarizes the results of the different cohort studies on the effect of smoking on joint damage.

Smoking & disability

More than one-third of RA patients have some form of early work cessation and loss of productivity [33]. Various studies have examined the impact of smoking on functional disability in RA patients. Some studies found a trend for greater disability in RA patients who smoke compared with never smokers [20,21], with a dose–response effect of cumulative smoking exposure on disability [14]. Other studies found no association between smoking and functional capacity [15–17,19,22,32], or the prevalence of work disability [34].

Smoking & response to treatment

Recently, interest has focused on the relationship between smoking and the response to antirheumatic therapy, since there seems to be a negative effect both on synthetic DMARD therapies, such as methotrexate, and on anti-TNF therapy. An early German study analyzed the influence of smoking on disease activity and drug need in a multicenter study of 896 patients with recent-onset RA [12]. The results showed that smokers had a younger disease onset and were more frequently RF positive, but had similar disease activity and disability compared with nonsmokers at baseline. However, at 3 years of follow-up, smokers had greater consumption of DMARD combinations and biologic therapies compared with never smokers. Smokers had also taken significantly more types of DMARDs, showed lower ACR improvement rates and less frequently achieved a good EULAR response. The authors suggested that these results may be due to the influence of smoking on basal metabolic rates, which are raised by systemic inflammation and further raised by smoking, which could result in shorter bioavailability of antirheumatic drugs. Three other groups have analyzed the relationship between the response to methotrexate therapy and tobacco smoking, and all found a reduced response to methotrexate in smokers [25,35,36]. Wessels *et al.* attempted to develop a model to predict the efficacy of methotrexate in monotherapy in RA after 6 months of treatment [35]. In the final model, smoking status (together with sex, RF and Disease Activity Score) was found to be a predictor of worse response to methotrexate. More recently, a subanalysis of the SWEFOT trial that searched for predictors of response to methotrexate therapy after 3–4 months of treatment in early DMARD-naive RA patients found that, in the multivariate analysis, current smoking, female sex, shorter symptom duration and younger age predicted a worse response to methotrexate [36]. A Mexican study aimed at determining factors associated with a non-ACR50 response at 6 months of follow-up in an early RA cohort treated with a combination therapy of methotrexate and sulfasalazine found that smoking was associated with a non-ACR50 response [22].

The response to biologic therapy in smokers, and especially to anti-TNF therapy, the most frequent first choice biologic therapy for RA patients, has also been thoroughly studied recently. Hyrich *et al.* were the first to examine the possible relationship between tobacco smoking and response to anti-TNF therapy [37]. They pointed out that, although anti-TNF therapy represents an important advancement in RA therapy, a significant proportion of patients (~30%) do not improve. They aimed to identify predictors of response to anti-TNF therapy in

RA patients. A total of 2879 patients receiving etanercept or infliximab were analyzed and the results showed an association between smoking and a poor outcome with infliximab, but not with etanercept. Subsequently, this relationship between anti-TNF and smoking was analyzed by other groups with similar results [38–40]. Abhishek *et al.* studied 395 patients and found that current smoking was a significant predictor of nonachievement of a moderate EULAR response after 3 months of anti-TNF therapy [38]. No differences were found in the response to treatment between nonsmokers and exsmokers. Another study analyzed the dose (pack/year) effect of smoking on the response to anti-TNF therapy [39] in the light of reports that the pack/year history was important in the risk of developing seropositive RA [6,41], with heavy smokers (>20 pack/year) having the greatest risk. The study found that, in smokers, there was a significant inverse relationship between improvement in disease activity at 3 months and the number of packs/year. Smokers of >30 packs/year were 5.8-times more likely to show no response to anti-TNF therapy at 3 months than nonsmokers. Failure to respond was associated with the intensity of previous smoking, irrespective of smoking status at initiation of therapy with TNF antagonists [39]. More recently, a study of a Swedish registry of 535 patients with early RA found that current smokers were less likely to respond to methotrexate and anti-TNF therapy [40], while a Portuguese registry of 617 patients that analyzed the effectiveness and predictors of response to anti-TNF therapy found that smoking and other factors predicted a reduced likelihood of response to treatment [42]. By contrast, one study that analyzed serum cotinine (the major metabolite of nicotine) as a biomarker of tobacco exposure and its association with RA therapy (methotrexate alone or in combination with other DMARDs or etanercept) in early RA patients found no relationship between serum cotinine and disease activity after 1 or 2 years of follow-up. However, smoking status was determined solely by the serum cotinine biomarker, which could lead to misclassification of passive smokers or patients using nicotine replacement therapy as current smokers and, in addition, the intensity of the exposure could not be quantified [43]. The relationship between other biologic therapies and smoking has only been examined in one study, which evaluated disease activity after 6 months of rituximab therapy in 150 consecutive patients and found a reduced response to therapy in current and previous smokers compared with never smokers [44]. A subanalysis of the BeSt study evaluated the impact of smoking on treatment response and found that smoking was an independent risk factor for the reactivation of RA and drug reintroduction in patients who discontinued anti-TNF (infliximab) after achieving persistent low disease activity [45]. A recent Berlin EULAR Congress communication also reported that smokers are more prone to disease flares after reduction of the anti-TNF dose due to clinical remission [46].

Evaluation of the response to antirheumatic treatment in smokers may be influenced by possible confounders including the socioeconomic status and coping mechanisms in smokers and nonsmokers. The level of formal education, which is analyzed in some studies, may be a surrogate marker of these variables. In one study, formal education of <6 years was associated with less probability of achieving an ACR50 response with anti-TNF treatment [25], although this was independent of smoking status. Other studies found no association between formal education and response to treatment [12,47]. In addition, differences in outcomes may have been overestimated due to differences in subjective measures in smokers versus nonsmokers. Analysis of these studies shows that smokers have higher visual analog scale and tender joint scores, and higher scores in other objective measures such as ESR and CRP or swollen joint count [12,47].

In summary, the available evidence suggests that smokers with early RA have a poorer response to methotrexate and biologic therapy, which could indicate that smokers have more persistent disease activity irrespective of the therapy used. Although there is no clear explanation for this, some hypotheses can be suggested. First, smokers have been shown to have an increased frequency of RF and ACPA [6,7,10,19,20,22,32,39,41,48], which is known to be associated with a poorer prognosis [32,49–52] and worse response to anti-TNF therapy in some studies [53–55]. Second, methotrexate polyglutamate concentrations, which have been reported to correlate with clinical response, but not toxicity, in RA, have been shown to be lower in active smokers than in noncurrent smokers [56]. Third, increased production of TNF-α by T cells in patients with RA who smoke has been described by an English group with an increase in the TNF-α:soluble TNF receptor ratio released by T cells that was associated with the pack/year history [57], and that remained elevated in past smokers. However, monocyte TNF-α release was not associated with smoking status. Another study found no significant differences between

smokers and nonsmokers in CRP and ESR levels at baseline or after 3 months of treatment, which could argue against the lack of response being due to an elevation of inflammatory mediators in smokers [39]. Finally, it has not been established whether smoking cessation prior to the initiation of treatment is beneficial or not. As mentioned, some studies found that past smokers responded as well as nonsmokers, although this requires further study. Table 2 summarizes the results of the different studies.

Conclusion

Smoking is the most accepted and well-studied risk factor for the development of seropositive RA, particularly in genetically-predisposed

Table 2. Studies on the therapeutic response in rheumatoid arthritis according to smoking status.

Study (year)	Study and cohort patients	Treatment	Results	Ref.
Hyrch *et al.* (2006)	2879 RA	Anti-TNF (ETN and IFX) 6 months	Current smoking status was a negative predictor of good EULAR response after 6 months of treatment with IFX, OR: 0.77 (95% CI: 0.60–0.99), but not ETN after multivariate analysis	[37]
Wessels *et al.* (2007)	205 eRA	MTX 6 months	Sex, RF status, smoking status, DAS at baseline, SJC, HAQ score and four genetic polymorphisms were independent predictors of response to MTX monotherapy at 6 months of treatment	[35]
Westhoff *et al.* (2008)	896 RA	DMARDs 3 years	Smokers (particularly those who smoked more than 20 packs/year) had significantly more types of DMARDs during the observation period	[12]
Mattey *et al.* (2009)	154 RA	Anti-TNF (ETN, IFX) 3 months	Smokers had a poor response to TNF antagonists, with significantly higher DAS28, HAQ and VAS pain at 3 months Response failure was associated with the intensity of smoking (pack/year)	[39]
Abhishek *et al.* (2010)	395 RA	Anti-TNF (ETN, IFX and ADA) 3 months	Smokers were less likely to respond to anti-TNF therapy when compared with nonsmokers, OR: 0.20 (95% CI: 0.05–0.83); p = 0.03	[38]
Saevarsdottir *et al.* (2011)	405 eRA	MTX 3 months	Current smoking was associated with less likelihood of response as defined by the SDAI, CDAI and ACR20 response criteria, as well as EULAR response after multivariate analysis, OR: 0.35 (95% CI: 0.20–0.63)	[36]
Saevarsdottir *et al.* (2011)	535 eRA	MTX and anti-TNF 3 months	Current smokers were less likely to respond to MTX (OR: 0.60; 95% CI: 0.39–0.94) and anti-TNF (OR: 0.52; 95% CI: 0.29–0.96). The influence of smoking did not differ between anti-CCP-positive and -negative patients	[40]
Rojas-Serrano *et al.* (2011)	142 eRA	MTX and SSZ 6 months	Smoking was associated with a non-ACR50 response in eRA treated with combination therapy of MTX and SSZ (smoking status OR: 3.91; 95% CI: 1.41–10.81; p < 0.009)	[25]
Söderlin (2012)	934 RA	Anti-TNF (ETN, IFX and ADA) 12 months	Current smoking was predictive of poor response to anti-TNF treatment Heavy smokers had the poorest drug survival	[47]
Canhao *et al.* (2012)	617 RA	Anti-TNF (ETN, IFX and ADA) 12 months	There were no differences in the effectiveness of all three anti-TNF (ETN, ADA and IFX) Smoking, the presence of anti-CCP, use of glucocorticoids and worse physical assessment of disease activity at baseline were predictors of reduced likelihood of treatment response	[42]
Maska *et al.* (2012)	412 eRA	DMARDs and ETN 2 years	Smoking status was not associated with response to triple DMARD therapy (MTX plus HCQ plus SSZ) or ETN plus MTX	[43]
Khan *et al.* (2012)	150 RA	Rituximab 6 months	Smokers had a worse response to treatment with rituximab, 98% of nonsmokers responded to rituximab treatment vs 61% of previous smokers and 20% of current smokers	[44]

ACR20: Percentage of study participants achieving 20% of the ACR response criteria; ACR50: Percentage of study participants achieving 50% of the ACR response criteria; ADA: Adalimumab; anti-CCP: Anticyclic citrullinated peptide antibodies; CDAI: Clinical Disease Activity Index; DAS: Disease Activity Score; DAS28: Disease Activity Score over 28 joint count; DMARD: Disease-modifying antirheumatic drug; eRA: early Rheumatoid Arthritis; ETN: Etanercept; EULAR: European League Against Rheumatism; HAQ: Health Assessment Questionnaire; HCQ: Hydroxychloroquine; IFX: Infliximab; MTX: Methotrexate; OR: Odds ratio; RA: Rheumatoid arthritis; RF: Rheumatoid factor; SDAI: Simple Disease Activity Index; SJC: Swollen joint count; SSZ: Sulfasalazine; VAS: Visual analog scale.

individuals, and might account for up to one-third of cases of seropositive AR. However, the effect of smoking on the clinical phenotype is not yet established. Smokers have a significantly earlier disease onset. The effect of smoking on disease activity at presentation and during follow-up is likewise not established since, as noted, studies show conflicting results, although this may be due to methodological differences. The effect of smoking on disease outcomes (disability and radiographic joint damage) is also unclear, with some studies finding that smoking determines a worse outcome and others that it does not. Longer-term studies, in larger cohorts, taking into account possible confounders such as serologic markers, genotype (the presence of the shared epitope – a determinant of RA outcomes) and the level of smoking exposure are required to establish the effects of smoking on RA outcomes. There is evidence that points towards a detrimental influence of smoking on RA, with a poorer prognosis in smokers. In addition, it seems that smoking may have an effect on the RA clinical phenotype and outcomes, although this is probably moderate and dose dependant. What seems clear is that smoking has a negative effect on the response to antirheumatic treatment, especially to methotrexate and anti-TNF therapy. The possible benefit of smoking cessation on RA outcomes remains an unanswered question.

The effect of smoking on RA is complex and requires extensive further research. The available evidence adds to the known impact of smoking on cardiovascular, pulmonary disease and an increased risk of malignancy. This alone requires health professionals to encourage RA patients to stop smoking.

Future perspective

The effect of smoking in the course of the disease is controversial and one of the main reasons for this is the differences in methodology. Prospective and well-designed studies focusing on the effects of tobacco on different outcomes such as disability or radiographic progression in early RA and taking into account the amount of cigarettes smoked and other prognostic markers is warranted. Smoking status should be incorporated in clinical trials as a prognostic marker of therapeutic response for both synthetic DMARDs and biologics. Clinical studies on the effect of smoking cessation in RA will be of interest. Experimental studies on the effect of smoking in the pathophysiology of RA may provide new insights into the molecular basis of this intriguing relationship.

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Executive summary

Background

- The development of rheumatoid arthritis (RA) is determined by the presence of genetic and environmental factors and the interaction between them.

Epidemiology

- Tobacco smoking is the most studied and widely accepted environmental risk factor for the development of seropositive (rheumatoid factor/anticyclic citrullinated peptide-positive) RA.

Smoking & RA clinical phenotype & outcomes

- The effect of smoking on different aspects of RA, such as disease presentation, disease activity, disability and joint damage (radiographic progression), is controversial.

Smoking & joint damage in RA

- Some evidence points towards a detrimental influence of smoking on RA, with a poorer prognosis and more joint damage in smokers.
- This effect is probably moderate and dose dependant.

Smoking & response to treatment in RA

- Recent data strongly suggest that smokers are less likely to respond to methotrexate and TNF antagonists than nonsmokers.

Conclusion

- Further studies are needed to better understand and determine the effect of smoking on RA outcomes.
- RA patients should be encouraged to stop smoking, as it not only increases the risk of cancer and cardiovascular and lung disease, but may also have a detrimental effect on RA outcomes.

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