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Objectives: To investigate whether smoking habits predict response to rituximab (RTX) in rheumatoid arthritis (RA).
Method: We included patients from the CERERRA international cohort receiving the first treatment cycle with available smoking status (n = 2481, smokers n = 528, non-current smokers n = 1953) and at least one follow-up visit. Outcome measures were change in Disease Activity Score based on 28-joint count (ΔDAS28) and European League Against Rheumatism (EULAR) good response at 6 months, with non-current smokers as the referent group.
Results: Compared with non-smokers at baseline, smokers were more often rheumatoid factor (RF)/anti-citrullinated protein antibody (ACPA) positive and males, had shorter disease duration, lower DAS28 and Health Assessment Questionnaire (HAQ) score, a higher number of prior biological disease-modifying anti-rheumatic drugs, and were more likely to receive concomitant conventional synthetic disease-modifying anti-rheumatic drug (csDMARDs). Disease activity had decreased less in smokers at 6 months (ΔDAS28 = 1.5 vs 1.7, p = 0.006), although the difference was no longer significant after correction for baseline DAS28 (p = 0.41). EULAR good response rates did not differ between smokers and non-smokers overall or stratified by RF/ACPA status, although smokers had lower good response rates among seronegative patients (ACPA-negative: 6% vs 14%, RF-negative: 11% vs 18%). Smoking did not predict good response [odds ratio (OR) = 1.04, 95% confidence interval (CI) = 0.76–1.41], while ACPA, DAS28, HAQ, and concomitant csDMARDs were significant predictors for good response. However, when stratified by country, smokers were less likely to achieve good response in Sweden (unadjusted OR = 0.24, 95% CI = 0.07–0.89), and a trend was seen in the Czech Republic (OR = 0.45, 95% CI = 0.16–1.02).
Conclusion: In this large, observational, multinational RA cohort, smokers starting RTX differed from non-smokers by having shorter disease duration and lower disease activity, but more previous treatments. The overall results do not support smoking as an important predictor for response to RTX in patients with RA.

The role of cigarette smoking in rheumatoid arthritis (RA) is multifaceted. It is a well-established risk factor for the development of RA, especially anti-citrullinated protein antibody (ACPA)-positive RA in genetically susceptible individuals (1). It has also been associated with increased occurrence of extra-articular manifestations (2) and with radiographic progression (3, 4), and it has been identified as an important negative predictor of response to anti-rheumatic therapy, including methotrexate and tumour necrosis factor inhibitors (TNFis) in several studies (4–6). So far, only a few studies have examined the association between smoking and

response to non-TNFi biological disease-modifying anti-rheumatic drugs (bDMARDs) (6, 7).

Rituximab (RTX) is a B-cell depleting agent which acts through binding to the CD20 molecule on the surface of B cells, and induces direct signalling of apoptosis, complement activation, and cell-mediated cytotoxicity (8). It is a chimeric monoclonal antibody and is approved for the treatment of active RA after the failure of one or more TNFis. Its efficacy and acceptable safety profile have been well established, both in randomized controlled trials and in observational studies (9–13). The approved dose of RTX consists of two infusions of 1000 mg administered with a 2 week interval, although data show that a lower dose may be equally efficient (14, 15). Some predictors of response to RTX have been identified, the strongest of them being the presence of autoantibodies, rheumatoid factor (RF), and ACPAs [usually measured with the anti-cyclic citrullinated peptide (anti-CCP) test] (13). Regarding the relationship between RTX effectiveness and smoking, one letter has been published on a small study group showing strong negative associations with response, using non-validated criteria (16).

The aim of this large observational study on RA patients from several European countries was to assess whether smoking status influences the clinical response to RTX, using outcome measures recommended by the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR), and with power to stratify into disease subsets and adjust for potential confounders.

Method

Patient population and selection

The European Collaborative Registries for the Evaluation of Rituximab in Rheumatoid Arthritis (CERERRA) is an investigator-led, industry-supported initiative with the aim of evaluating the clinical aspects of RTX use in patients with RA. The following participating European registries submitted fully anonymized data sets of patients with a diagnosis of RA who had started treatment with RTX: Czech Republic, Denmark, Finland, Norway, Portugal, Russia, Slovenia, Sweden, and Switzerland. It was a retrospective observational study, but the data were collected prospectively. Data were analysed both stratified per country and pooled. Ethical approval for the use of register data from each register was obtained by local authorities of each country. The Regional Ethical Review Board in Stockholm approved the collection and analysis of anonymized data from the participating registers. Informed consent was obtained from each patient before inclusion in each register, according to local regulations.

Patients starting treatment with RTX regardless of dose (most received 1 g ×2; a smaller percentage received 500 mg

× 2) were identified. The following information was collected at baseline, which was defined as time of first RTX treatment: demographic data (age, gender); RA disease duration in years (from the time of RA diagnosis); RF (positive/negative); ACPA (positive/negative); number of prior conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), and number of prior bDMARDs; Disease Activity Score based on 28-joint status (DAS28) and its components (swollen joint count, tender joint count, visual analogue scale general health and erythrocyte sedimentation rate, the latter except for Danish patients in whom only C-reactive protein was available); functional status based on the Health Assessment Questionnaire (HAQ); and concomitant glucocorticoid and csDMARD use. DAS28 and HAQ as well as information on concomitant corticosteroid and csDMARD use were reported at every follow-up visit. Smoking status was defined as cigarette smokers (current smokers) and non-smokers (never and ex-smokers). This information was only collected at RTX start, except for the Swedish study population, where information about smoking status (at diagnosis) was available for patients who also participated in the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) (6).

Patients with available baseline smoking status and at least one follow-up visit were included in the current analysis. Response to the first treatment cycle was assessed. Patients who were lost to follow-up or patients who started treatment with RTX very close to the time of the data pooling and therefore had not yet had a follow-up visit were excluded. Last observation carried forward (LOCF) was used to handle missing DAS28 values for patients who had a follow-up visit but not a DAS28 assessment (i.e. patients not lost to follow-up).

Statistical analysis

Data were collected longitudinally. Different time-frames for follow-up were created: 3 (± 1) and 6 (± 1) months. For duplicate data (patients with two or more visits within a time-frame) the last observation was included. We prioritized 6 month over 3 month data, when available, but when no such data were available, we used data from the 3 month visit.

Baseline characteristics were compared between smokers and non-smokers by means of descriptive statistics. The normality of variables was tested by skewness. Normally distributed continuous variables are presented as mean ± sd, while those with a non-normal distribution are presented as median (interquartile range). Student's t-test and Mann–Whitney U-test were used to compare continuous variables, while the chi–squared test was used for nominal variables. The level of statistical significance was set to 5%.

Three main analyses were performed. First, the effectiveness of RTX during the first 6 months after the first treatment cycle was compared between smokers and non-smokers, with Disease Activity Score (DAS28) as the main outcome measure, using standard approaches:

Table 1. Comparison of baseline demographic, disease, and treatment characteristics for rituximab-treated rheumatoid arthritis patients in non-smokers versus smokers.

Characteristic	Non-smokers (N = 1953)	Smokers (N = 528)	Difference between groups (p)
Age (years), mean ± sd	52.7 ± 13.1 [1949]	52.6 ± 11.7 [528]	0.99
Gender, % female	85.9 [1953]	62.5 [528]	< 0.0001
Disease duration (years), median (IQR)	10.0 (5.0–16.0) [1918]	7.4 (3.9–13.0) [518]	< 0.0001
RF, % positive	79.9 [1819]	84.8 [514]	0.01
ACPA, % positive	79.4 [957]	84.6 [325]	0.04
Baseline DAS28, mean ± sd	5.7 ± 1.5 [1855]	5.2 ± 1.6 [489]	< 0.0001
Baseline HAQ, mean ± sd	1.6 ± 0.7 [1558]	1.4 ± 0.7 [395]	< 0.0001
No. of prior csDMARDs, mean ± sd)	2.6 ± 1.5 [1882]	2.4 ± 1.4 [496]	0.12
No. of prior bDMARDs, median (IQR)	1.0 (0–1.0) [1953]	1.0 (0–2.0) [528]	< 0.0001
Concomitant GCs	61.1 [1886]	58.3 [496]	0.25
Dose (mg), median (IQR)	7.5 (5.0–10.0) [1046]	7.5 (5.0–10.0) [231]	0.72
Concomitant csDMARDs	80.0 [1953]	84.8 [528]	0.01

The numbers in square brackets represent the total number of patients with available information.
IQR, interquartile range; RF, rheumatoid factor; ACPA, anti-citrullinated peptide antibodies; DAS28, Disease Activity Score based on 28 joint count and four variables; HAQ, Health Assessment Questionnaire; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; bDMARDs, biological disease-modifying anti-rheumatic drugs; GCs, glucocorticoids.

(i) changes in levels on a continuous scale [reduction of DAS28 from baseline (ΔDAS28)], (ii) the EULAR response criteria (good, moderate, no), and (iii) the target of remission (DAS28 < 2.6) or low disease activity (LDA) (DAS28 ≤ 3.2). For continuous outcomes, the two groups were compared by the Student's t-test and by linear regression with adjustment for baseline imbalances. Adjusted analyses were only conducted when the crude p value was < 0.05. Fisher's exact test was used for nominal outcomes. Separate stratified analyses were performed for the RF and anti-CCP-positive and -negative disease subsets.

Secondly, logistic regression analysis was performed with EULAR good response at 6 months as the dependent variable and smoking as the independent variable, for the whole cohort and for each register separately (sensitivity analysis). Several other known or potential predictors of response to RTX (see Table 4) were tested using univariate logistic regression and then in multivariate analysis models. By means of stepwise backward selection, each of these covariates was excluded from the model until only statistically significant variables remained. RF and ACPA were included separately in the model because of strong collinearity between them.

Thirdly, the number of follow-up visits was not the same for all patients, and the time interval between visits was not the same for all patients and even for the same patient, as expected in a real-life setting. For these reasons, mixed-models analyses were also performed; mixed-model analysis is a preferable method for analysing such longitudinal data, as it can handle uneven spacing of repeated measurements and even missing data (as long as missing data are missing at random). A mixed-effects model with ΔDAS28 as the dependent variable and baseline smoking status as the fixed effect was performed to assess the effectiveness of treatment according to smoking. Time was also fitted in the model as

1/time. The interaction smoking * (1/time) was also included in the model. Country and patient were included in the model as random variables. In a second step, several potential confounders [age, gender, disease duration, number of prior bDMARDs, concomitant csDMARDs, baseline DAS28 and HAQ, RF, and ACPA (the last two separately)] were included in the models. Different association models for the covariance structure between the repeated measures of the primary outcomes were performed and compared using the Akaike information criterion. Smoking groups were also compared by estimated marginal means.

Results

More than 5000 patients were included in the CERERRA cohort until the year 2014 and they served as the basis for the current analyses. After exclusion of patients without smoking status or with only a baseline visit, 2481 patients were included in the analyses, of whom 1953 were identified as non-smokers (never or ex-smokers) and 528 as smokers (current). Significant heterogeneity across countries was observed regarding the proportion of smokers and other characteristics (Supplementary Tables S1 and S2). Baseline characteristics of patients stratified for smoking status are summarized in Table 1. Smokers were more often male, and had shorter disease duration, lower disease activity, lower functional impairment, a higher number of previous bDMARDs, and more often concomitant csDMARD treatment compared to non-smokers.

Effectiveness of RTX according to smoking status

At 6 months' follow-up, non-smokers had a significantly larger DAS28 reduction from baseline (Table 2). However, this was not significant after correction for baseline DAS28

Table 2. Effectiveness of rituximab treatment at 6 months in non-smokers and smokers.

			Difference between groups	
	Non-smokers (N = 1953)	Smokers (N = 528)	Crude p-value	Adjusted p-value*
DAS28 6 months	4.2 ± 1.4 (1552)	4.0 ± 1.4 (394)	0.02	
ΔDAS28 6 months	−1.7 ± 1.6 (1516)	−1.5 ± 1.6 (382)	0.006	0.44
EULAR response 6 months	[1360]	[308]	0.95	
Good	19.6%	20.1%		
Moderate	53.9%	52.9%		
No	26.5%	26.9%		
Remission/LDA 6 months	24.1% [1552]	28.2% [394]	0.10	

The numbers in square brackets represent the total number of patients with available information.
DAS28, Disease Activity Score based on 28-joint count; EULAR, European League Against Rheumatism; LDA, low disease activity.
*Adjusted analyses were conducted only when the crude p value was < 0.05.

in the regression analysis (Table 2). In addition, no significant differences in EULAR response or remission rate were observed overall between smokers and non-smokers (Table 2).

After stratification for RF and ACPA status (Table 3), no significant differences in response to RTX between smokers and non-smokers were observed, apart from a significantly higher percentage of patients achieving remission/LDA in smokers compared to non-smokers among RF-positive patients (30.6% vs 24.8%, p = 0.04). However, some numerical differences were observed, for example a higher EULAR good response rate and a higher remission/LDA rate in non-smokers than in smokers among ACPA-positive (p = 0.53 and p = 0.22) and ACPA-negative patients (p = 0.52 and p = 0.51).

Predictors of response

In the univariate logistic regression analysis (Table 4), smoking status was not predictive for EULAR good response to RTX after 6 months [unadjusted odds ratio (OR) = 1.04, 95% confidence interval (CI) 0.76–1.41]. However, because of the heterogeneity between the patient populations included from the participating countries (Supplementary Table S2), we conducted a sensitivity analysis

stratified by country and found that smoking was a significant predictor of less response to RTX in the Swedish study group (OR = 0.24, 95% CI 0.07–0.89, p = 0.03) and there was a trend in the register from the Czech Republic (OR = 0.45, 95% CI 0.16–1.02, p = 0.06), while in the other registers there was a trend towards a better response in smokers (data not shown).

In a multivariate analysis including ACPA and other known or potential predictors using a stepwise backward selection, only the following two characteristics were significant predictors of good response: a lower number of prior bDMARDs (OR = 0.63, 95% CI 0.44–0.91, p = 0.01) and ACPA positivity (OR = 2.34, 95% CI 1.47–3.75, p < 0.0001). In a different multivariate model with RF (but without ACPA), RF positivity (OR = 1.44, 95% CI 1.01–2.05, p = 0.04), lower baseline DAS28 (OR = 0.85, 95% CI 0.77–0.94, p = 0.002), and no concomitant glucocorticoids at baseline (OR = 0.70, 95% CI 0.53–0.92, p = 0.01) were independent predictors of EULAR good response at 6 months.

Longitudinal analyses of response by smoking

During the first 6 months from baseline, 2958 and 822 follow-up visits were recorded for non-smokers and

Table 3. Effectiveness of rituximab treatment at 6 months in non-smokers and smokers stratified by anti-citrullinated protein antibody (ACPA) and rheumatoid factor (RF) status.

	ACPA positive		ACPA negative		RF positive		RF negative	
	Non-smokers	Smokers	Non-smokers	Smokers	Non-smokers	Smokers	Non-smokers	Smokers
EULAR response 6 months	[524]	[187]	[151]	[33]	[986]	[242]	[261]	[52]
Good	26.5%	21.9%	13.9%	6.1%	19.9%	21.9%	17.6%	11.5%
Moderate	47.7%	49.2%	51.0%	57.6%	54.5%	51.2%	52.1%	57.7%
No	25.8%	28.9%	35.1%	36.4%	25.7%	26.9%	30.3%	30.8%
Remission/LDA months	29.4%	27.6%	22.3%	15.8%	24.8%	30.6%	22.0%	17.5%
						(p = 0.04)		

The numbers in square brackets represent the total number of patients with available information. Analyses are unadjusted.
EULAR, European League Against Rheumatism; LDA, low disease activity.

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Table 4. Predictors of European League Against Rheumatism (EULAR) good response at 6 months.

Independent variable	OR (95% CI)	p
Smoking (smokers vs non-smokers)	1.04 (0.76–1.41)	0.82
Gender (male vs female)	1.33 (0.98–1.80)	0.07
Age (per year increase)	1.00 (0.99–1.01)	0.83
RA disease duration (per year increase)	0.99 (0.97–1.00)	0.13
Prior csDMARDs (number)	0.93 (0.85–1.02)	0.13
Prior bDMARDs (0–1 vs > 1)	0.85 (0.61–1.16)	0.30
RF (positive vs negative)	1.28 (0.92–1.77)	0.15
ACPA (positive vs negative)	2.37 (1.49–3.79)	< 0.0001
Baseline DAS28 (per unit increase)	0.87 (0.79–0.96)	0.004
Baseline HAQ (per unit increase)	0.79 (0.65–0.95)	0.01
Concomitant GCs (yes vs no)	0.65 (0.51–0.84)	0.001
Concomitant csDMARDs (yes vs no)	1.02 (0.74–1.41)	0.89

RA, rheumatoid arthritis; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; bDMARDs, biological disease-modifying anti-rheumatic drugs; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies; DAS28, Disease Activity Score based on 28-joint count; HAQ, Health Assessment Questionnaire; GC, glucocorticoids; OR, odds ratio; CI, confidence interval.

smokers, respectively. In the mixed-model analyses with ΔDAS28 as the dependent variable, time (1/time) and smoking status as fixed factors, and country and individual patient as random factors, the interaction between smoking and time was not statistically significant (p = 0.22) (Figure 1). Estimated marginal means for non-smokers and smokers were −1.69 (95% CI −1.76; −1.61) and −1.42 (95% CI −1.57; −1.26), respectively (p = 0.002). However, the difference disappeared when the model was adjusted for baseline differences between smokers and non-smokers. In the final model, higher baseline DAS28 (p < 0.0001), male gender (p = 0.02), RF positivity (p = 0.05), and lower number of

prior bDMARDs (p < 0.0001) were significantly associated with ΔDAS28 during this period. Smoking was not significant (p = 0.36). Estimated marginal means for non-smokers and smokers were −1.60 (95% CI −1.69; −1.50) and −1.58 (95% CI −1.72; −1.44), respectively (p = 0.83). The same analysis was performed with ACPA instead of RF, with similar results. No signs of effect modification of RF or ACPA were found in the mixed-model analyses stratified according to RF and ACPA status (data not shown).

Discussion

In this large, prospective, real-life cohort from several European countries, smoking was not associated with response to treatment with RTX in RA patients overall, and only marginal differences were observed in subgroups. This is in contrast to what has been shown for TNFi and even csDMARDs (methotrexate and combination therapies), the effectiveness of which is negatively correlated with current smoking (4–6). However, it was also evident that smokers differed from non-smokers, since they had shorter disease duration and lower disease activity at the start of treatment, and had tested more treatments before, indicating a more severe disease course, in accordance with numerous previous studies on smoking and long-term outcome in RA (4, 17–19).

In a letter published by Khan et al with 150 patients, non-smoking was strongly associated with response to RTX, in addition to RF positivity, ACPA positivity, and baseline DAS28 (16). Non-smokers had very high response rates (≥ 98%) to RTX irrespective of their RF/ACPA status, while current and previous smokers only achieved response rates of ≥ 50% if they were seropositive. This was, however, a small study, and the definition of response was a decrease in DAS28 of ≥ 1.2 after 6 months of treatment in patients with initial DAS28 scores > 5.1. There have been no other studies confirming these findings. In our study, we could not differentiate between the response of smokers and non-
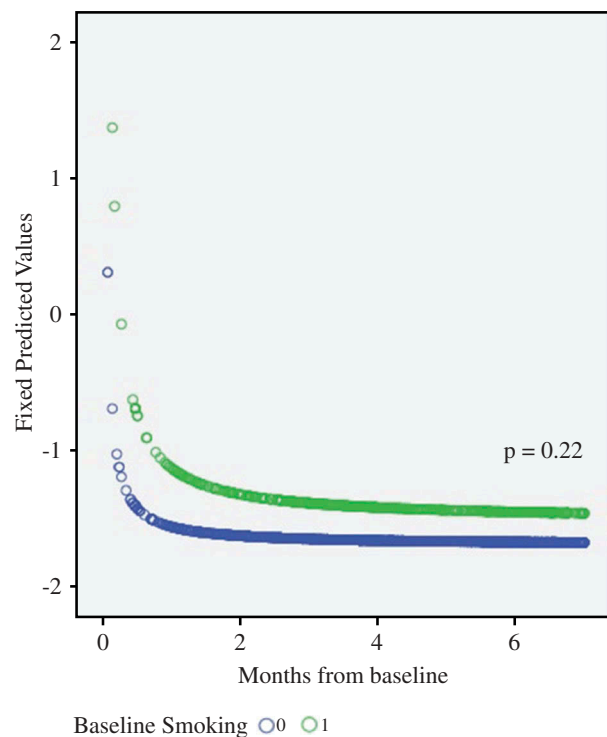

Figure 1. Unadjusted fixed predicted change in 28-joint Disease Activity Score for smokers and non-smokers (mixed-model analysis).

smokers, and there was no sign of effect modification by RF and ACPA status (Table 2).

A 2015 study, published in abstract form, examined the relationship of smoking and response to tocilizumab, an anti-interleukin-6 receptor monoclonal antibody (7). These preliminary results indicate no negative effect of smoking on clinical response. This discrepancy between smoking and different bDMARDs, TNFi and non-TNFi bDMARDs may imply different mechanisms behind the negative association with smoking. There is increasing evidence that the development of neutralizing anti-drug antibodies may be the reason for inefficacy (especially secondary inefficacy or loss of efficacy) in a significant number of patients treated with TNFis, especially infliximab and adalimumab (20). There is, to date, no evidence for such a mechanism for RTX or tocilizumab. In a 2014 study from Sweden, smoking was associated with an increased risk of development of anti-natalizumab antibodies in patients with multiple sclerosis (21). Thus, anti-drug antibody formation could be one explanation for the discrepancy observed between the effect of smoking habits on response to TNFi and non-TNFi bDMARDs and the evidence that exists today. However, this is only a hypothesis and remains to be further studied.

Another point that has to be taken into consideration is the major discrepancies observed across countries. In this study, smoking was a negative predictor of good response to RTX treatment in the Swedish cohort and a similar trend was observed in the cohort from the Czech Republic, but no significant association was observed in any other registers. There is a need for multicentre, international, prospective studies with both TNFis and non-TNFi-bDMARDs, to examine the real association between smoking and clinical response regardless of potential confounders, such as country and cultural differences across nations.

This study confirmed previous results regarding the positive predictive value for good response to RTX treatment of ACPA positivity, lower number of prior bDMARDs, and absence of concomitant glucocorticoids (13). Since ACPA is also associated with smoking (1), it is an important confounder to take into consideration when examining response to RTX treatment, including it in the multivariate analyses. To account for effect modification, stratified analyses by ACPA (and by RF) status were performed. Smoking was not associated with response to RTX, in either ACPA-positive or ACPA-negative patients.

This study has several limitations that need to be addressed. It is an observational study, and the risk of residual confounding even after correction for potential confounders is present. Information about smoking status was available for a subset of patients and was collected at baseline, that is, treatment start for all countries but Sweden, where the information was available at diagnosis. Since a strong association was observed in the Swedish subset only, one plausible explanation for the discrepancy is that smoking cessation occurring after diagnosis but before starting RTX could influence the findings, since we could not look separately at never and past smokers. We do not know what happened during the observational period, for example whether some patients changed their smoking habits, although if that happened it would most likely be for a minority of patients, as we know from clinical practice and previous studies (22). This is a multinational cohort, and significant heterogeneity is found across countries. We tried to account for this by including country as a random variable in the mixed-effect model analyses, as well as performing sensitivity analyses stratified by country. Missing data is a common problem with observational studies. We used LOCF for DAS28 in cases of missing DAS28 in patients who had a follow-up visit. We also used mixed-model analyses, which handle missing data. The lack of radiological data is also a limitation.

However, significant strengths of this study are the large number of patients, which provides enough power to detect potential differences between groups and to adjust for potential confounders; the real-life nature of the data, which increases the external validity of the results; and the fact that countries with cultural differences and different treatment protocols provided data.

Conclusion

Current smoking habits had very limited impact on disease activity and response to RTX in this large, observational, multinational RA cohort. However, smokers had several baseline characteristics indicating more severe disease, such as more previous treatments tested, despite shorter disease duration, and a lower baseline disease activity, possibly indicating other reasons for treatment start, such as a radiographic progression, about which we did not have information. Thus, a validation study in a trial-based setting is warranted. Although our findings do not support the notion that smoking cessation will increase the likelihood of response to RTX, it should be stressed that RA patients have many other reasons to quit smoking, for example to reduce their risks of a more destructive disease course, extra-articular manifestations, and cardiovascular comorbidities.

Disclosure statement

No potential conflict of interest related to this study was reported by the authors.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1. Proportion of smokers and non-smokers in each country participating in the CERERRA collaboration.
Supplementary Table S2. Baseline characteristics of patients stratified for smoking status in each register participating in the CERERRA collaboration.

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