The Journal of Rheumatology 2021;48:1504–7
doi:10.3899/jrheum.200213
First Release June 15 2021

The Journal of Rheumatology

Current Smoking Negatively Affects the Response to Methotrexate in Rheumatoid Arthritis in a Dose-responsive Way, Independently of Concomitant Prednisone Use

Mary Safy-Khan[1], Maria J.H. de Hair[2], Paco M.J. Welsing[1], Jacob M. van Laar[1], and Johannes W.G. Jacobs[1], on behalf of the Society for Rheumatology Research Utrecht (SRU)

ABSTRACT. ***Objective.*** Current smoking reduces clinical response to several disease-modifying antirheumatic drugs. It is unknown if this is also the case for prednisone. We aimed to determine whether current smoking affects the clinical response to concomitant prednisone in a methotrexate (MTX)-based treatment strategy.

Methods. In the CAMERA-II trial (isrctn.com identifier: 70365169), patients with early rheumatoid arthritis (RA) initiated an MTX-based strategy and were randomized to concomitant prednisone (MTX + pred) or placebo (MTX + PBO) for 24 months. Linear mixed modeling was performed with Disease Activity Score assessing 28 joints (DAS28) as the dependent variable, and strategy group and current smoking status as independent variables, correcting for relevant covariates. The interaction between current smoking and strategy was tested to find out whether the effect of current smoking on clinical response was different between the strategy groups with prednisone or PBO.

Results. Current smoking was significantly associated with higher DAS28 over time (mean difference with nonsmokers 0.57 [95% CI 0.22–0.92, $P < 0.01$]). This association was not different between the strategy groups with prednisone or PBO ($P = 0.73$). The negative effect of current smoking on DAS28 was dose dependent.

Conclusion. Current smoking in patients with early RA significantly reduces the clinical effect of an MTX-based strategy, independent of whether concomitant prednisone is used. This effect is dose dependent.

Key Indexing Terms: glucocorticoids, methotrexate, response, rheumatoid arthritis, smoking

Smoking is a known risk factor for the development of rheumatoid arthritis (RA),[1,2] and has been negatively associated with clinical response to several disease-modifying antirheumatic drugs (DMARDs).[3,4,5,6] For example, in the Swedish Farmacotherapy (SWEFOT) study and the U-Act-Early trial, current smoking negatively predicted the likelihood of response to methotrexate (MTX) in early RA.[3,4] In the U-Act-Early trial, this association was dose dependent.[4] Smoking was also found to be negatively associated with clinical response to rituximab (RTX) and anti–tumor necrosis factor (anti-TNF) treatment.[5,6] As far as we know, the association of smoking and clinical response to glucocorticoids (GCs) has never been studied, whereas concomitant GC treatment in RA is common in daily clinical practice. Early RA patients at initiation of MTX treatment often receive concomitant GCs[7] to further reduce disease activity and radiographic progression and improve functional ability.[8,9] For example, in the second Computer Assisted Management in Early Rheumatoid Arthritis trial (CAMERA-II), disease activity improved faster and erosive joint damage was significantly less in the MTX strategy group with prednisone, compared to the MTX strategy group with placebo (PBO), showing benefit of concomitant prednisone.[9] However, it has been found that approximately 30% of patients have a reduced or absent clinical response to GCs.[10,11] This might be associated with smoking, similar to the negative effects of smoking on the efficacy of other DMARDs. The primary objective of this study was to determine if the added clinical benefit of prednisone, when used concomitantly with MTX, is reduced among smokers.

METHODS

We used data from the CAMERA-II trial (isrctn.com identifier: 70365169), in which 236 patients with early RA were randomized to a treatment strategy initiating MTX and prednisone 10 mg/day (MTX + pred) or MTX and PBO (MTX + PBO). In short, MTX treatment was started at 10 mg/week and a tight control and treat-to-target strategy was followed with patient-tailored dosing adjustments at monthly visits on the basis of

[1]*M. Safy-Khan, MD, P.M. Welsing, PhD, J.M. van Laar, MD, PhD, Professor, J.W. Jacobs, MD, PhD, Associate Professor, Department of Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht University;* [2]*M.J. de Hair, MD, PhD, Novartis Pharma BV, the Netherlands.*

JMvL received honoraria from MSD, Roche, Pfizer, BMS, and Eli Lilly. MSK was supported by a research grant from AstraZeneca; AstraZeneca was not involved in this study. MJdH is an employee of Novartis Pharma BV; Novartis was not involved in this study. JWGJ and PMJW report no competing interests.

Address correspondence to M. Safy-Khan, PhD student, Department of Rheumatology & Clinical Immunology, G02.228, University Medical Center Utrecht, Box 85500, 3508 GA, Utrecht, the Netherlands.
Email: marysafy@hotmail.com.

Accepted for publication January 19, 2021.

predefined response criteria aiming for remission. If no remission was achieved at 4 weeks after reaching the maximum (tolerable) MTX dosage, the route of MTX administration was switched from oral to subcutaneous, and if thereafter still no remission was achieved, adalimumab was added. Prednisone or PBO was given in stable dose for 24 months. Details have been described previously.[9]

Ethics approval. The CAMERA-II trial was approved by the medical ethical committee of the University Medical Center Utrecht (medical ethical committee number: 02/042) and by the institutional review boards of all involved hospitals. The following Dutch hospitals were involved: University Medical Center Utrecht, Diakonessenhuis, Utrecht; St. Antonius Hospital, Nieuwegein; Meander Medical Center, Amersfoort; Tergooi Hospital, Hilversum; St. Jansdal Hospital, Harderwijk; and Flevohospital, Almere, the Netherlands. Patients gave written informed consent before entering the study.

Statistical analyses. For the present analyses, data were used on treatment strategy, current smoking status (yes/no), current smoking level (0, 1–9, 10–19, and ≥ 20 cigarettes/day), BMI (kg/m^2), sex, rheumatoid factor (RF) status, MTX and biological DMARD use, and Disease Activity Score assessing 28 joints (DAS28) at baseline and monthly up to 24 months. We used linear mixed modeling with a random intercept, DAS28 over 24 months' follow-up as the dependent variable; current smoking status and strategy group as independent variables; and DAS28 at baseline, time (trial months), time^2 (nonlinear course of DAS28 over time), BMI, sex, and RF status as covariates. In Model 1, we analyzed whether the effect of current smoking status (yes/no) on clinical response was different for MTX + pred when compared to MTX + PBO. To this end, the interaction term of group allocation and current smoking status was added to the model. Model 2 was similar to Model 1, but here we used the categorical variable of the different levels of current smoking as covariate in the model instead of the binary current smoking status variable, to evaluate the presence of a dose-response effect. Also, unadjusted data are shown on the course of DAS28 in each strategy arm of the CAMERA-II trial, separately for current smokers and nonsmokers (Figure 1). We used a random intercept at patient level (i.e., for the variable patient ID) to account for the dependence of repeated measurements over time, and the other variables were added as fixed effects in the model. These were current smoking status, sex, group allocation, RF status, DAS28 based on erythrocyte sedimentation rate at baseline, time, and BMI; further, the interaction terms time*time, and current smoking status*group allocation were entered in the model. We used a log-likelihood test to assess if the model fitted the data well. All analyses were performed with SPSS version 26 (IBM Corp.). All tests were 2-sided and $P \leq 0.05$ was considered statistically significant.

RESULTS

Current smoking data was available for 213 of 236 patients of the CAMERA-II trial. The baseline characteristics of these 213 patients were similar between the MTX + pred and MTX + PBO strategy groups (Table 1). Current smoking was significantly associated with a smaller reduction of DAS28 over time compared to current nonsmoking (β 0.57, 95% CI 0.22–0.92, $P < 0.01$; Table 2). This association was not statistically different between the MTX + pred and MTX + PBO strategy groups (P value for interaction term of treatment strategy and current smoking status = 0.73). In line with this, Figure 1 shows a clear effect of current smoking on the course of DAS28 that is of similar magnitude in each of the 2 strategy arms. The regression coefficient for BMI in the model was 0.03 (95% CI 0.00–0.06, $P = 0.04$; Table 2).

The association between current smoking and DAS28 over time was dose dependent: β 0.38 (95% CI –0.27 to 1.02, $P = 0.25$) for patients who smoked 1–9 cigarettes, β 0.59 (95% CI 0.06–1.12, $P = 0.03$) for patients who smoked 10–19 cigarettes, and β 0.66 (95% CI 0.18–1.13, $P < 0.01$) for patients who smoked ≥ 20 cigarettes per day (Table 2). The interaction terms between treatment strategy and current smoking levels were (again) not statistically different between the MTX + pred and MTX + PBO strategy groups. The model fitted the data well ($P < 0.00001$).

DISCUSSION

To our knowledge, this is the first study investigating the association of current smoking with the clinical effect of concomitant prednisone in RA. In this study in patients with early RA,

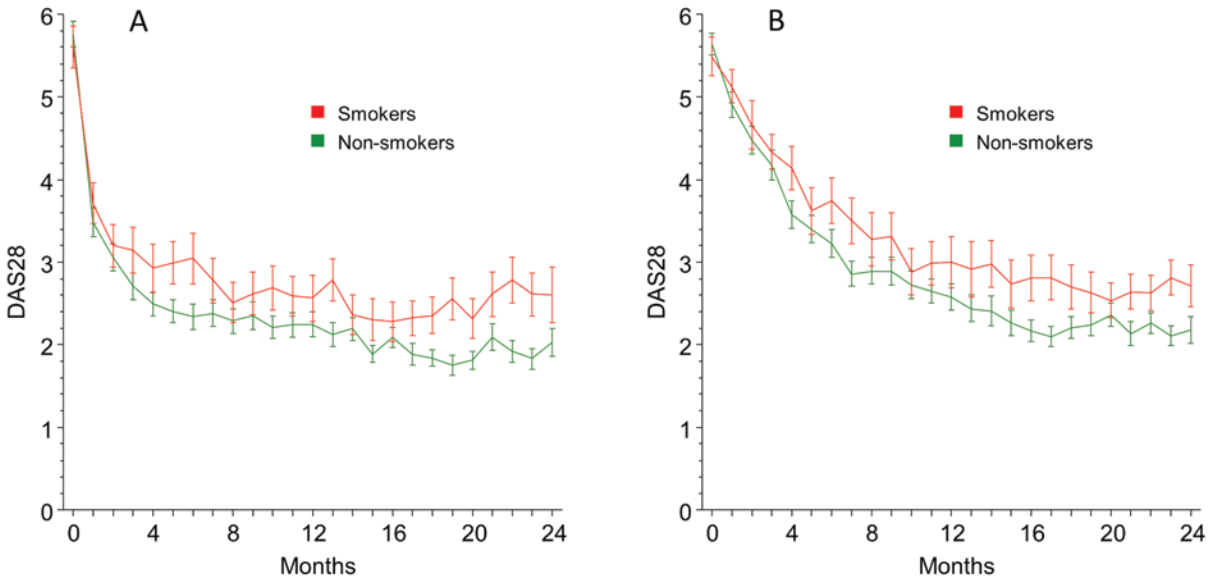

Figure 1. DAS28 over time for current smokers vs nonsmokers in each strategy arm of CAMERA-II. (A) Strategy initiating methotrexate with prednisone. (B) Strategy initiating methotrexate with placebo-prednisone. DAS28: Disease Activity Score assessing 28 joints.

Table 1. Baseline characteristics for each strategy arm group*.

	MTX + PBO, n = 109	MTX + Pred, n =104
Female sex, n (%)	66 (61)	60 (58)
Age, yrs, mean (SD)	54 (13)	54 (14)
DAS28, mean (SD)	5.7 (1.2)	5.8 (1.4)
RF-positive, n/N (%)	63/89 (71)	45/85 (53)
Smoking, n (%)	31 (28)	38 (37)
BMI, kg/m^2, mean (SD)	26 (4)	26 (4)
VAS GH, mm, mean (SD)	54 (25)	56 (23)
TJC28, median (IQR)	9 (6–13)	10 (5–18)
SJC28, median (IQR)	10 (6–15)	11 (6–15)
ESR, mm/h, median (IQR)	30 (15–49)	30 (15–47)
CRP, mg/L, median (IQR)	17 (8–45)	16 (0–44)

Baseline characteristics of 213 of the 236 patients included in CAMERA-II, for whom smoking data were available. * No statistically significant differences between the 2 groups. CRP: C-reactive protein; DAS28: Disease Activity Score assessing 28 joints; ESR: erythrocyte sedimentation rate; MTX: methotrexate; PBO: placebo; Pred: prednisone; RF: rheumatoid factor (n/N indicates number of patients with positive RF status of those with available RF status); SJC28: swollen joint count assessing 28 joints, range 0–28; TJC28: tender joint count assessing 28 joints, range 0–28; VAS GH: visual analog scale of global health (VAS range 0–100 mm, with 100 mm signifying the worst status).

we found a negative effect of current smoking on DAS28 for MTX-based strategies, independent of concomitant use of prednisone; this effect was dose dependent. These findings corroborate previously found negative associations between current smoking and response to MTX treatment in patients with early RA.[4,12] BMI had a (small) effect additionally to current smoking.

As MTX is often used in daily clinical practice,[7] our results emphasize the importance of nonsmoking in patients with early RA treated with MTX in clinical practice. Patients who smoke also have worse responses to RTX and anti-TNF treatment,[5,6] which many patients require later on in the disease course.[13,14] Not smoking or smoking cessation have other positive effects, such as on cardiovascular risk, which is especially important as this risk is increased in RA.[15,16,17]

The smaller reduction of disease activity over time induced by current smoking is not statistically significantly different between MTX + pred and MTX + PBO; this would indicate that the effect of prednisone is not statistically significantly influenced by current smoking. However, we cannot rule out (in)direct interactions between MTX and prednisone under current smoking and inflammatory conditions. If we compare our results in RA with those in other chronic diseases, such as in patients with asthma, no difference in effect of GCs on relapse rate has been shown for smokers and nonsmokers.[18] Also, in a study with 18 healthy male adults, no statistically significant effect of smoking on systemic availability of prednisolone was observed.[19]

The strength of our analysis is the use of data from a PBO-controlled trial, enabling the comparison of the association of current smoking with clinical response to prednisone and PBO-prednisone. Further, our study examined the relatively long-term effect (i.e., over 24 months) of current smoking on treatment response to MTX as well as concomitant prednisone, whereas other studies examined the effect of current smoking on treatment effect to MTX only, and only up to a maximum of 6 months of treatment.[3,6]

Our study has limitations. The negative association between current smoking and clinical response might partly be explained

Table 2. Smoking as predictor and DAS28 over time (24 months) as outcome: 2 models.

	Model 1: Smoking Yes/No *β (95% CI)*	*P*		Model 2: Smoking Level *β (95% CI)*	*P*
Smoking (vs nonsmoking)	0.57 (0.22–0.92)	< 0.01	Smoking level, cigarettes/day		
			0	Ref	
			1–9	0.38 (–0.27 to 1.02)	0.25
			10–19	0.59 (0.06–1.12)	0.03
			≥ 20	0.66 (0.18–1.13)	< 0.01
Male sex (vs female)	–0.45 (–0.69 to –0.21)	< 0.01	Male sex (vs female)	–0.49 (–0.74 to 0.24)	< 0.01
RF positivity (vs RF negativity)	0.08 (0.34 to –0.17)	0.51	RF positivity (vs RF negativity)	0.05 (0.30 to –0.21)	0.71
DAS28, baseline	0.41 (0.32–0.50)	< 0.01	DAS28, baseline	0.41 (0.32–0.50)	< 0.01
Time	–0.31 (–0.32 to –0.29)	< 0.01	Time	–0.31 (–0.32 to –0.29)	< 0.01
BMI	0.03 (0.00–0.06)	0.04	BMI	0.03 (0.00–0.06)	0.06
Time*time	0.01 (0.01–0.01)	< 0.01	Time*time	0.01 (0.01–0.01)	< 0.01
Group allocation: MTX + pred (vs MTX + PBO)	–0.65 (–1.06 to –0.24)	< 0.01	Group allocation: MTX + pred (vs MTX + PBO)	–0.74 (–1.03 to –0.46)	< 0.01
Group allocation*smoking interaction	0.09 (–0.41 to 0.58)	0.73	Group allocation*smoking level interaction, cigarettes/day		
			0	Ref	
			1–9	–0.17 (–1.05 to 0.71)	0.71
			10–19	–0.25 (–1.04 to 0.54)	0.54
			≥ 20	0.12 (–0.56 to 0.80)	0.73

The results of the 2 models, corrected for DAS28 at baseline, time (trial months), time^2, BMI, sex, and RF status. A positive estimate reflects a higher DAS28 over time. DAS28: Disease Activity Score assessing 28 joints; MTX: methotrexate; PBO: placebo; pred: prednisone; RF: rheumatoid factor.

by anticyclic citrullinated peptide status, but this status had not been assessed in CAMERA-II. However, this does not diminish the clinical relevance of our findings. Data on current smoking for almost 10% of patients were missing. However, as there is no reason to assume that these missing data were not at random, it is unlikely that they have influenced our findings. The number of participating patients was limited, so it cannot be ruled out that current smoking would have a minor negative effect on the benefit of prednisone, but our results show that a clinically relevant effect is absent.

Our finding that current smoking negatively affects the clinical response to MTX-based strategies and that this negative current smoking effect is not different if concomitant prednisone is used, warrants validation, although circumstantial evidence supports this finding.

ACKNOWLEDGMENT

The Society for Rheumatology Research Utrecht (SRU) centers that participated in the CAMERA-II trial included: University Medical Center Utrecht, Antonius Hospital Nieuwegein, Diakonessen hospital Utrecht, Gelre ziekenhuizen Apeldoorn, Meander Medical Center Amersfoort, Maartenskliniek Woerden, St. Jansdal Harderwijk, and Tergooi ziekenhuizen Hilversum.

DATA SHARING

Request for data access can be directed to the corresponding author.

REFERENCES

1. Klareskog L, Stolt P, Lundberg K, Källberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 2006;54:38-46.
2. Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2010;69:70-81.
3. Saevarsdottir S, Wallin H, Seddighzadeh M, Ernestam S, Geborek P, Petersson IF, et al; SWEFOT Trial Investigators Group. Predictors of response to methotrexate in early DMARD naive rheumatoid arthritis: results from the initial open-label phase of the SWEFOT trial. Ann Rheum Dis 2011;70:469-75.
4. Teitsma XM, Jacobs JWG, Welsing PMJ, de Jong PHP, Hazes JMW, Weel AEAM, et al. Inadequate response to treat-to-target methotrexate therapy in patients with new-onset rheumatoid arthritis: development and validation of clinical predictors. Ann Rheum Dis 2018;77:1261-7.
5. Khan A, Scott DL, Batley M. Smoking, rheumatoid factor status and responses to rituximab. Ann Rheum Dis 2012;71:1587-8.
6. Saevarsdottir S, Wedrén S, Seddighzadeh M, Bengtsson C, Wesley A, Lindblad S, et al. Patients with early rheumatoid arthritis who smoke are less likely to respond to treatment with methotrexate and tumor necrosis factor inhibitors: observations from the Epidemiological Investigation of Rheumatoid Arthritis and the Swedish Rheumatology Register cohorts. Arthritis Rheum 2011;63:26-36.
7. Smolen JS, Landewé R, Bijlsma JWJ, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying anti-rheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960-77.
8. Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309-18.
9. Bakker MF, Jacobs JW, Welsing PM, Verstappen SM, Tekstra J, Ton E, et al; Utrecht Rheumatoid Arthritis Cohort Study Group. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. Ann Intern Med 2012;156:329-39.
10. Barnes PJ, Adcock IM. Glucocorticoid resistance in inflammatory diseases. Lancet 2009;373:1905-17.
11. Stanczyk PS. The effect of methylprednisolone on proliferation of PBMCs obtained from steroid-sensitive and steroid-resistant rheumatoid arthritis patients. Scand J Rheumatol 2009;36:167-71.
12. Rojas-Serrano J, Pérez LL, García CG, Moctezuma F, Álvarez-Hernández E, Vázquez-Mellado J, et al. Current smoking status is associated to a non-ACR 50 response in early rheumatoid arthritis. A cohort study. Clin Rheumatol 2011;30:1589-93.
13. Soliman MM, Ashcroft DM, Watson KD, Lunt M, Symmons DP, Hyrich KL; British Society for Rheumatology Biologics Register. Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2011;70:583-9.
14. Rein P, Mueller RB. Treatment with biologicals in rheumatoid arthritis: an Overview. Rheumatol Ther 2017;4:247-61.
15. Boyer JF, Gourraud PA, Cantagrel A, Davignon JL, Constantin A. Traditional cardiovascular risk factors in rheumatoid arthritis: a meta-analysis. Joint Bone Spine 2011;78:179-83.
16. Soubrier M, Barber Chamoux N, Couderc M, Dubost JJ, Mathieu S. Cardiovascular risk in rheumatoid arthritis. Joint Bone Spine 2014;81:298-302.
17. Puttevils D, De Vusser P, Geusens P, Dens J. Increased cardiovascular risk in patients with rheumatoid arthritis: an overview. Acta Cardiol 2014;69:111-8.
18. Schuckman H, DeJulius DP, Blanda M, Gerson LW, DeJulius AJ, Rajaratnam M. Comparison of intramuscular triamcinolone and oral prednisone in the outpatient treatment of acute asthma: a randomized controlled trial. Ann Emerg Med 1998;31:333-8.
19. Rose JQ, Yurchak AM, Meikle AW, Jusko WJ. Effect of smoking on prednisone, prednisolone, and dexamethasone pharmacokinetics. J Pharmacokinet Biopharm 1981;9:1-14.