Alcohol is not the missing link between *Porphyromonas gingivalis*-related periodontitis and radiological progression in early rheumatoid arthritis: comment on '*Porphyromonas gingivalis* experimentally induces periodontitis and an anti-CCP2-associated arthritis in the rat'

We have read with great interest the paper from Courbon *et al* providing the first in vivo demonstration of arthritis induced by oral priming with *Porphyromonas gingivalis* in rats, though an increased prevalence of periodontal diseases has been observed in rheumatoid arthritis (RA) for a century.[1] This major agent of periodontal disease is one of the only bacterium known to express a peptidylarginine deiminase. Citrullinated epitopes, generated by its enzymatic activity, bind to HLA-DRB1*04:01/04 with higher affinity than uncitrullinated epitopes, leading to an enhanced T-cell response [2] and trigger the production of anti-citrullinated protein antibody (ACPA).

Alcohol consumptio is a major risk factor for chronic periodontitis. Interestingly, two articles suggested an association between long-term moderate alcohol drinking and reduced risk of RA onset.[3] Moreover, an inverse relationship between moderate alcohol consumption and radiological progression was suggested in men with early RA but not in women in two independent RA patient cohorts.[4]

Therefore, we investigated relationship between *P. gingivalis* infection, alcohol consumption, gender and radiological progression in American College of Radiology/European League Against Rheumatism (ACR/EULAR) 2010 early RA patients of the ESPOIR cohort (ethic no 020307).

Patients presented with inflammatory arthritis of at least two swollen joints lasting for 6 weeks to 6 months, who were not exposed to steroids or disease-modifying antirheumatic drugs and fulfilling ACR/EULAR 2010 RA criteria at inclusion were included. *P. gingivalis* infection was measured at baseline by serum levels of anti-*P. gingivalis* antibodies.[5] Radiological progression was defined as a progression ≥1 point/year of modified Sharp/van der Heijde score within the first 5 years of follow-up.[5] Smoking status and alcohol consumption were respectively collected as dichotomous and quantitative (in grams/day) variable at all visits up to 5 years as previously described.[4]

A total of 533 patients with early RA fulfilling 2010 ACR/EULAR criteria were included; 417 (78%) patients were female, mean age was 50 years (online supplementary table 1). A total of 266 (50%) patients were ACPA positive and 282 (53%) were rheumatoid factor (RF) positive; C reactive protein (CRP) was increased in 372 (70%) patients. A total of 93 (18%) patients had erosive RA at baseline, and 409 (77%) patients had radiological progression at 5 years. A total of 133 patients (25%) were seropositive at baseline for *P. gingivalis*. About 246 (46%) patients were active smokers. About 90 (17%) patients were alcohol consumers. Among them, 30 (6%) patients were considered alcohol abusers (>20 g/day for women and >30 g/day for men).[4]

We did not observe any difference of baseline demographics characteristics in *P. gingivalis* seropositive and seronegative patients (table 1). The adjusted OR (table 2) and the multivariate analysis (online supplementary table 1) did not find any significant interaction between *P. gingivalis* serology, alcohol consumption, gender and radiological progression.

Hence, the beneficial role of alcohol consumption on radiological progression in men with RA [4] was not explained in our study by interaction with *P. gingivalis* seropositivity. One of the limits of our study is our assay of *P. gingivalis* infection. Anti-*P. gingivalis* ELISA is robust for assessing long-term exposure to *P. gingivalis* but is not associated with current active infection, and its titre is not a reliable proxy of bacterial burden.[5] However, our assay showed increased titres of anti-*P. ginvivalis* antibodies in patients with periodontal disease, who constitute a relevant positive control group.[5] Quantitative PCR could be considered for future

Table 1 Description and univariate analysis of potential interaction factors of ACR/EULAR 2010 early RA patients in the ESPOIR cohort at baseline

N=533	*Porphyromonas gingivalis* serology positive (n=133)	*P. gingivalis* serology negative (n=399)	P value	Female (n=417)	Male (n=116)	P value
Gender, male	112 (84.2)	309 (77.3)	0.43	–	–	–
Age, years	50.4 (42.7 to 57.0)	50.0 (38.2 to 57.1)	0.39	49.6 (39.8 to 56.9)	53.1 (41.5 to 58.1)	0.06
Active smoking	62 (46.6)	186 (46.5)	0.65	169 (40.5)	77 (66.4)	<0.01
Alcohol consumers*	30 (22.5)	63 (15.8)	0.08	55 (13.2)	38 (32.7)	<0.01
DAS28	5.41 (4.6 to 6.4)	5.3 (4.6 to 6.1)	0.95	5.36 (4.6 to 6.2)	5.3 (4.7 to 6.3)	0.99
RF positive†	80 (60.1)	204 (51)	0.19	223 (53.5)	59 (50.9)	0.62
ACPA positive†	68 (51.1)	199 (49.8)	0.81	202 (48.4)	64 (55.2)	0.20
CRP above ULN†	93 (69.9)	282 (70.5)	0.33	279 (66.9)	93 (80.2)	<0.01
Baseline erosion	21 (15.7)	72 (18.0)	0.39	66 (15.8)	27 (23.3)	0.06
Radiological progression‡	97 (72.9)	311 (76.2)	0.23	313 (76.5)	96 (23.5)	0.083
Positive *P. gingivalis* serology	–	–	–	112 (26.86)	26 (22.4)	0.43

Data are presented as number (%) and mean (95% CI).

*Alcohol consumers were patients with alcohol intake >0 g/day (ie, patients with moderate consumption defined as ≤20 g/day for women and ≤30 g/day for men) and alcohol abusers: >20 g/day for women and >30 g/day for men. Baseline alcohol consumption was used for the primary outcome.[5]

†Patients were considered RF, ACPA positive or CRP above ULN when baseline assay was above the ULN. *P. gingivalis* antibodies were measured using a home-made ELISA as previously described.[5] Patients were considered *P. gingivalis* positive when their anti-*P. gingivalis* antibody titre was above the higher quartile.

‡Radiological progression was defined as a progression ≥1 point/year of modified Sharp/van der Heijde score within the first 5 years of follow-up.

ACPA, anti-citrullinated protein antibody; ACR/EULAR, American College of Radiology/European League Against Rheumatism; CRP, C-reactive protein; DAS28, Disease Activity Score 28 joints; RA, rheumatoid arthritis; RF, rheumatoid factor; ULN, upper reference limit.

Table 2 Interactions between gender, *Porphyromonas gingivalis* infection and radiological progression of ACR/EULAR 2010 early rheumatoid arthritis patients in the ESPOIR cohort

N=533		Alcohol abstinent (n=440)	Alcohol consumption (n=93)	OR (95% CI), p value	
Men (n=116)	No radiological progression	14 (3)	6 (1)	1.17 (0.41 to 3.32), p=0.774	0.31 (0.19 to 0.50), p<0001
	Radiological progression	64 (12)	32 (6)		
Women (n=417)	No radiological progression	93 (17)	11 (2)	1.38 (0.84 to 2.63), p=0.364	
	Radiological progression	269 (50)	44 (9)		
Negative *P. gingivalis* serology (n=399)	No radiological progression	78 (15)	10 (2)	1.60 (0.79 to 3.30), p=0.198	1.55 (0.95 to 2.52), p=0.075
	Radiological progression	258 (48)	53 (10)		
Positive *P. gingivalis* serology (n=133)	No radiological progression	29 (6)	7 (1)	1.28 (0.50 to 3.25), p=0.602	
	Radiological progression	74 (14)	23 (4)		
Women and positive *P. gingivalis* serology (n=107)	No radiological progression	27 (5)	3 (1)	1.82 (0.48 to 6.94), p=0.372	
	Radiological progression	64 (12)	13 (2)		
Men and positive *P. gingivalis* serology (n=26)	No radiological progression	2 (0)	4 (1)	0.50 (0.07 to 3.37) p=0.481	
	Radiological progression	10 (2)	10 (2)		
Women and negative *P. gingivalis* serology (n=309)	No radiological progression	66 (12)	8 (2)	1.25 (0.55 to 2.86), p=0.591	
	Radiological progression	204 (39)	31 (6)		
Men and negative *P. gingivalis* serology (n=90)	No radiological progression	12 (2)	2 (0)	2.44 (0.51 to 11.83), p=0.257	
	Radiological progression	54 (10)	22 (4)		

Data are presented as number (%) and mean (95% CI).
P. gingivalis antibodies were measured using a home-made ELISA as previously described.[5] Patients were considered *P. gingivalis* positive when their anti-*P. gingivalis* antibody titre was above the higher quartile.
Smoking status and alcohol consumption were, respectively, collected as dichotomous and quantitative (in grams/day) variable at all visits up to 5 years as previously described according to the classification of the WHO.[4] Alcohol abstinent: 0 g/day; moderate consumption defined as ≤20 g/day for women and ≤30 g/day for men, and alcohol abusers: >20 g/day for women and >30 g/day for men. Baseline alcohol consumption was used for the primary outcome.
Radiological progression was defined as a progression ≥1 point/year of modified Sharp/van der Heijde score within the first 5 years of follow-up.
OR (95% CI) calculated for interaction between gender and *P. gingivalis* seropositivity were adjusted for baseline alcohol consumption. Mantel–Haenszel test was applied to determine the level of significance.
ACR/EULAR, American College of Radiology/European League Against Rheumatism.

studies to provide a better evaluation of bacterial activity in periodontal disease associated with RA and possible further opportunity for RA treatment as non-surgical periodontal treatment decreases both *P. ginvivalis*-related periodontal disease and disease activity of RA.[6]

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