Alcohol is not the missing link between Porphyromonas gingivalis-related periodontitis and radiological progression in early rheumatoid arthritis

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 consumption 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 (etno 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.⁶ 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.⁵

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 (23%) 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).³ 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. gingivalis antibodies in patients with periodontal disease, who constitute a relevant positive control group.⁵ Quantitative PCR could be considered for future 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. gingivalis-related periodontal disease and disease activity of RA.⁶

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

<table>
<thead>
<tr>
<th>N=533</th>
<th>Porphyromonas gingivalis serology positive (n=133)</th>
<th>Porphyromonas gingivalis serology negative (n=399)</th>
<th>P value</th>
<th>Female (n=417)</th>
<th>Male (n=116)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male</td>
<td>112 (84.2)</td>
<td>309 (77.3)</td>
<td>0.43</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age, years</td>
<td>50.4 (42.7 to 57.0)</td>
<td>50.0 (38.2 to 57.1)</td>
<td>0.39</td>
<td>49.6 (39.8 to 56.9)</td>
<td>53.1 (41.5 to 58.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Active smoking</td>
<td>62 (46.6)</td>
<td>186 (46.5)</td>
<td>0.65</td>
<td>169 (40.5)</td>
<td>77 (66.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Alcohol consumers</td>
<td>30 (22.5)</td>
<td>63 (15.8)</td>
<td>0.08</td>
<td>55 (13.2)</td>
<td>38 (32.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DAS28</td>
<td>5.41 (4.6 to 6.4)</td>
<td>5.3 (4.6 to 6.1)</td>
<td>0.95</td>
<td>5.36 (4.6 to 6.2)</td>
<td>5.3 (4.7 to 6.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>RF positive</td>
<td>80 (60.1)</td>
<td>204 (51)</td>
<td>0.19</td>
<td>223 (53.5)</td>
<td>59 (50.9)</td>
<td>0.62</td>
</tr>
<tr>
<td>ACPA positive</td>
<td>68 (51.1)</td>
<td>199 (49.8)</td>
<td>0.81</td>
<td>202 (48.4)</td>
<td>64 (55.2)</td>
<td>0.20</td>
</tr>
<tr>
<td>CRP above ULN</td>
<td>93 (69.9)</td>
<td>282 (70.5)</td>
<td>0.33</td>
<td>279 (66.9)</td>
<td>93 (80.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Baseline erosion</td>
<td>21 (15.7)</td>
<td>72 (18.0)</td>
<td>0.39</td>
<td>66 (15.8)</td>
<td>27 (23.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Radiological progression</td>
<td>97 (72.9)</td>
<td>311 (76.2)</td>
<td>0.23</td>
<td>313 (78.5)</td>
<td>96 (82.5)</td>
<td>0.083</td>
</tr>
<tr>
<td>Positive P. gingivalis serology</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>112 (26.86)</td>
<td>26 (22.4)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

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

1 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.

2 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. ³ Patients were considered P. gingivalis positive when their anti-P. gingivalis antibody titre was above the higher quartile.

4 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 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

<table>
<thead>
<tr>
<th>Gender (n=533)</th>
<th>Alcohol abstinent (n=440)</th>
<th>Alcohol consumption (n=93)</th>
<th>OR (95% CI), p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (n=116)</td>
<td>No radiological progression 14 (3)</td>
<td>6 (1)</td>
<td>1.17 (0.41 to 3.32), p=0.774</td>
</tr>
<tr>
<td></td>
<td>Radiological progression 64 (12)</td>
<td>32 (6)</td>
<td>0.31 (0.19 to 0.50), p&lt;0001</td>
</tr>
<tr>
<td>Women (n=417)</td>
<td>No radiological progression 93 (17)</td>
<td>11 (2)</td>
<td>1.38 (0.84 to 2.63), p=0.364</td>
</tr>
<tr>
<td></td>
<td>Radiological progression 269 (50)</td>
<td>44 (9)</td>
<td>1.55 (0.95 to 2.52), p=0.075</td>
</tr>
</tbody>
</table>

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

Porphyromonas gingivalis antibodies were measured using a home-made ELISA as previously described. 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. 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 Rheumatology/European League Against Rheumatism.

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Acknowledgements The authors thank the Direction de la Recherche Clinique et de l’innovation of CHU Grenoble Alpes for its support. An unrestricted grant from Merck Sharp and Dohme was allocated for the first 5 years. Two additional grants from INSERM were obtained based on the biological database. The French Society of Rheumatology, Pfizer, Abbvie, Roche-Chugai also supported the ESPOIR cohort study. The authors also wish to thank Nathalie Rincheval (CHU Montpellier and EA 2415) who did expert monitoring and data management and all the investigators who recruited and followed the patients (P Bierenbaum, Paris-Saint Antoine; M C Boissier, Paris-Boibigny; A Cantagrel, Toulouse; B Combe, Montpellier; M Dougdas, Paris-Cochin; F Fardelone and P Bournier Amiens; B Fautrel, Paris-La Pitié; M FIlipo, Lille; Ph. Goupille, Tours; F Liote, Paris- Lariboisière; O Vittecoq, Rouen; X Mariette, Paris Bicêtre; O Meyer et Ph Dieude, Paris Bichat; A Saraux, Brest; Th Schaeaverbeke, Bordeaux; J Sibilla, Strasbourg); V Devachelle and C Lukas for expert X-ray reading and S Martin (Paris Bichat) who did all the central dosages of CRP, IgA and IgM RF and anti-CCP antibodies. The authors also thank Pr Maurice Dematteis for fruitful comments on our study.

Collaborators Bruno Fautrel and Xavier Mariette.

Contributors JH wrote the manuscript; interpreted statistical analysis; AB generated statistical analysis and critically reviewed the study proposal; XR served as scientific advisors and critically reviewed the study proposal; FS served as scientific advisors and critically reviewed the study proposal; GF served as scientific advisors and critically reviewed the study proposal; PG served as scientific advisors and critically reviewed the study proposal; AB generated statistical analysis and critically reviewed the study proposal; JR served as scientific advisors and critically reviewed the study proposal; FS served as scientific advisors and critically reviewed the study proposal; BF served as scientific advisors and critically reviewed the study proposal; PG served as scientific advisors and critically reviewed the study proposal; FS served as scientific advisors and critically reviewed the study proposal; BB served as scientific advisors and critically reviewed the study proposal; PP served as scientific advisors and critically reviewed the study proposal; JH and AB contributed equally.

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Received 11 May 2019
Accepted 15 May 2019
Published Online First 14 June 2019

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

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Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2019-215603).

JH and AB contributed equally.

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