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Role of good oral hygiene on clinical evolution of rheumatoid arthritis: a randomized study nested in the ESPOIR cohort

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Abstract

Objective. There is a relationship between RA and periodontal disease. We aimed to investigate if a good oral hygiene could improve activity of RA.

Methods. The patients with RA according to ACR/EULAR 2010 criteria and included in the French early arthritis ESPOIR cohort were included in a randomized nested study into: (i) intervention group: general recommendations of good oral hygiene including teeth brushing, daily antiseptic mouthwash and twice a year scaling; and (ii) control group: no intervention. The primary end point was the delta DAS28-ESR.

Results. Four hundred and seventy-two patients were randomized (238 in intervention and 234 in control). 92/238 from the intervention group accepted the procedure and 81 had a first visit to the dentist. 56% of patients had periodontal disease at baseline. Duration of RA was 9.0±0.7 years. Baseline DAS28-ESR was 2.7±1.3. After a median duration of 24 months, delta DAS28-ESR was −0.17±1.29 and −0.09±1.28 in intervention and control groups, respectively (mean difference (complier average causal effect): −0.37 (95% CI −1.12, 0.37), $P = 0.33$). In the intervention group, there was a significant decrease of the bacteria involved in the red complex: *Porphyromonas gingivalis* ($P = 0.002$), *Tannerella forsythia* ($P = 0.002$) and *Treponema denticola* ($P = 0.019$). The patients with baseline periodontal disease and those who became negative for one red complex bacterium had a slightly more important decrease of DAS28-ESR.

Conclusion. Oral hygiene instruction together with regular scaling and polishing of the teeth significantly decreased the load of periodontal pathogens but did not decrease RA activity. This intervention should be tested in patients with earlier RA and more active disease.

Trial registration. ClinicalTrials.gov, http://clinicaltrials.gov, NCT01831648.

Key words: rheumatoid arthritis, periodontal disease, *Porphyromonas gingivalis*, treatment

Rheumatology key messages

- In patients with established RA, good oral hygiene with regular scaling of the teeth did not decrease RA activity.
- The patients with baseline periodontal disease had a slightly more important decrease of DAS28-ESR.
- Good oral hygiene allowed a significant decrease of gengival *Porphyromonas gingivalis* load.

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Introduction

There is substantial evidence for a relationship between RA and periodontal disease (PD). Several epidemiological studies have suggested a link between periodontal disease and RA. The prevalence of periodontal disease is two-fold increased among patients with RA compared with the general population [1–3], and even more in non-smoking RA patients with a four-fold increased prevalence [4]. In addition, several cohorts have shown that the risk of development of RA was increased in subjects with PD [5–7]. This risk was even more important in non-smokers [7].

CLINICAL SCIENCE

This bidirectional association is biologically supported by studies suggesting that some bacteria involved in PD may play a role by inducing some inflammatory features specific of RA. *Porphyromas gingivalis (Pg)*, a gram-negative oral anaerobe, is a periodontal pathogen that belongs to the red complex, which is an important player in the pathogenicity of PD. *Pg* is one of the rare microorganisms with a peptidyl arginine deiminase capable of transforming arginine into citrulline, and is thus suspected to play a role in the production of ACPA. A number of studies have suggested that the presence of *Pg* was associated with development of RA, particularly ACPA-positive RA [8–13]. Nevertheless, the association of *Pg* with RA has not been found in all studies [3, 14–16], and was obtained from small cohorts for most of them. Nevertheless, a recent meta-analysis found a statistically significant association between the titre of anti-*Pg* antibodies and RA, even though the confidence intervals of mean odds-ratios were not given [17]. Moreover, *Pg* experimentally induces PD and an anti-CCP2-associated arthritis in the rat [18]. On the other hand, *Aggregatibacter actinomycetemcomitans (Aa)*, a periodontal pathogen associated with PD severity, has been suspected to be the culprit of the association of RA and PD [16]. In this study, *Aa* and not *Pg* was associated to RA. *Aa* was able to induce citrullinated antigens in neutrophils by inducing netosis through leukotoxin A, a specific toxin from this bacterium. However, the association of anti-leukotoxin A antibodies and RA was not confirmed in a large Dutch study [19]. Thus, the biological explanation of the epidemiological association between RA and PD remains to be elicited.

Periodontal prevention is a key component of oral health. It aims at lowering the oral bacterial load. To achieve this goal, mechanical and chemical dental plaque controls have been advocated over time. Chemical plaque control is based on the daily use of mouth rinses and fluoride-containing toothpastes, whereas the mechanical approach includes both individual and professional tooth cleaning, that is, tooth brushing and scaling, respectively. This intervention corresponds to the guidelines of good oral hygiene in the general population from both the American Dental Association (www.mouthhealthy.org/en/oral-health-recommendations) and the European Federation of Periodontology (www.efp.org/perio-workshop/workshop-2014/guidelines/Prevention-of-periodontal-diseases-general-guidance.pdf). Nowadays, there is no evidence that an adequate home oral care together with a regular scale and polish may improve clinical activity of RA.

We aimed to investigate if home oral care recommendations associated with a regular professional plaque control could reduce the activity of RA, by setting-up the Buccal HYgiene and Reduction of activity of RA (BHYRRA) study, a randomized trial nested in the French Evaluation et Suivi des POlyarthrites Indifférenciées Récentes (ESPOIR) cohort of patients with established RA.

Methods

Inclusion criteria

All patients with RA included in the ESPOIR cohort and still followed in 2013 were included in the study. ESPOIR is a prospective French cohort that included 813 patients with early arthritis. The methodology and the main characteristics of the patients from the ESPOIR cohort have been previously described [20]. Fourteen regional centres in France participated in patients' inclusion. The patients were recruited if they had inflammatory arthritis of at least two swollen joints lasting for 6 weeks to 6 months and with potential to evolve into RA. Patients were included if they had not received DMARDs (except within the 15 days before inclusion in the cohort for DMARDs exclusively) or steroids. Patients were excluded if the referring physician considered another defined inflammatory rheumatic disease than RA. The patients were included between December 2002 and March 2005. They have been followed every 6 months during the first 2 years, and every year thereafter. The follow-up is scheduled for at least 20 years from December 2002. Among them, 694 fulfilled the 2010 ACR/EULAR criteria after 2 years of follow-up and 472 were still followed after 10 years in 2013.

Clinical and biological assessment

Clinical variables included total joint count for tenderness and swelling, the DAS in 28-joints (DAS28) [21]. Laboratory variables included ESR (mm/h), CRP (mg/l) level, IgM and IgA RF (both ELISA [Menarini], both positive if $>$ 9 UI/ml), ACPA (anti-CCP2, ELISA, DiaSorin, France; positive if $>$ 50 U/ml).

Study design and intervention

BHYRRA is a randomized trial nested in the French ESPOIR cohort following the cohort multiple randomized controlled trial design [22]. All the RA patients still followed at 10 years were randomized into two groups:

- Intervention group: treated according to a periodontal care programme including: (i) tooth brushing twice a day with a dentifrice (Colgate Total®, Colgate-Palmolive, Colombes, France); (ii) mouth rinse once a day with an antiseptic mouthwash (Listerine®, Johnson and Johnson, Issy les Moulineaux, France); (iii) scaling and polishing by a periodontist twice a year.
- Control group: no specific intervention and no specific information were given to the patients.

In both groups the treatment of RA was conducted according to the decision of the physician.

Bacterial sampling

In the intervention group, an identification and quantification of nine periodontal pathogens in the gingival pockets was made by the periodontist at the first scaling visit (M0) and 12 months after this first scaling (M12). They include the following: *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythensis, Treponema denticola, Prevotella intermedia, Peptostreptococcus micros, Fusobacterium nucleatum, Campylobacter rectus* and *Eikenella corrodens.* The Perio-Analyse® sampling kit was used according to the manufacturer's instructions (Institut Clinident, www.institut-clinident.com/). This is a real-time PCR technique that extracts bacterial DNA from gingival

crevicular fluid collected with absorbent paper points inserted between the gingival and the tooth surface.

The protocol of the ESPOIR cohort study was approved in 2002 by the Ethics Committees of Montpellier University Hospital (No. 020307). All patients included in ESPOIR gave their written informed consent.

Regarding BHYRRA, as what was proposed was only to follow the recommendations for good oral hygiene from the general population, no informed consent was asked from the patients. The study is registered as ClinicalTrials.gov identifier: NCT01831648 and was approved by the local ethics committee.

Endpoints

The primary end point was the delta DAS28-ESR between post and pre-randomization visits in both groups. DAS28-ESR was collected during ESPOIR visits. For patients who received the intervention, the post-randomization visit was the ESPOIR visit occurring immediately after second scaling. If the second scaling was not performed, the ESPOIR visit closest from the first scaling +12 months was selected. Due to the delay between randomization and planification of the first scaling, the median delay between randomization and post-randomization visit was 21 months (interquartile range (IQR): [17; 26]). For patients who did not receive the intervention, the post-randomization visit was the ESPOIR visit occurring immediately after randomization (median delay of 6 months after randomization, IQR: [4; 9]). To consider the difference of delay between the two groups, pre-randomization visits for the control group were randomly selected according to the distribution of delays in the intervention group.

Gingival bacterial load (total number of bacteria) of the nine bacteria was collected at the first scaling visit (M0) and 12 months after this visit (M12).

Statistical analyses

To acknowledge the expected high number of intervention refusal among patients randomized to the intervention group (in particular because they had a regular follow-up with their own dental practitioner and/or because the location of the referral dental centre was too far from their home), the primary analysis was a complier average causal effect (CACE) analysis using an instrument variable (IV) approach. CACE represents the treatment effect in the hypothetical subgroup of patients who would have planned their first visit whatever their randomization group. The IV approach is valid if there is no effect of the instrument on the outcome other than that mediated through the treatment (exclusion restriction assumption). Accordingly, delta DAS28-ESR was analysed using a two-stage least squares model with randomization as the instrumental variable and planification of the first visit as the treatment variable. A subgroup analysis of the primary outcome according to anti-CCP status of patients was pre-specified. Missing data for the primary outcome were handled through multiple imputations by chained equations.

In a post-hoc analysis, the delta DAS28-ESR was also estimated in patients who became PCR negative for one of the three bacteria of the red complex if initially positive at baseline.

To assess if the procedure could decrease bacterial load, the total number of each of the nine bacteria was compared before and after intervention with paired Student's t-tests.

For all analyses, a $P < 0.05$ was considered statistically significant. Confidence intervals were calculated at the 95% level. Statistical analyses involved use of R 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients' characteristics

Four hundred and seventy-two patients from the ESPOIR cohort were randomized, 238 in the intervention group and 234 in the control group. As expected, only 92/238 from intervention group accepted the procedure and 81/92 had a first visit to the dentist. The flow chart of the study is presented in Fig. 1. Baseline characteristics of RA were not different between intervention and control groups (Table 1). Characteristics of the 81 patients of the intervention group who had their first visit to the dentist and of the 157 who had not are also presented in Table 1.

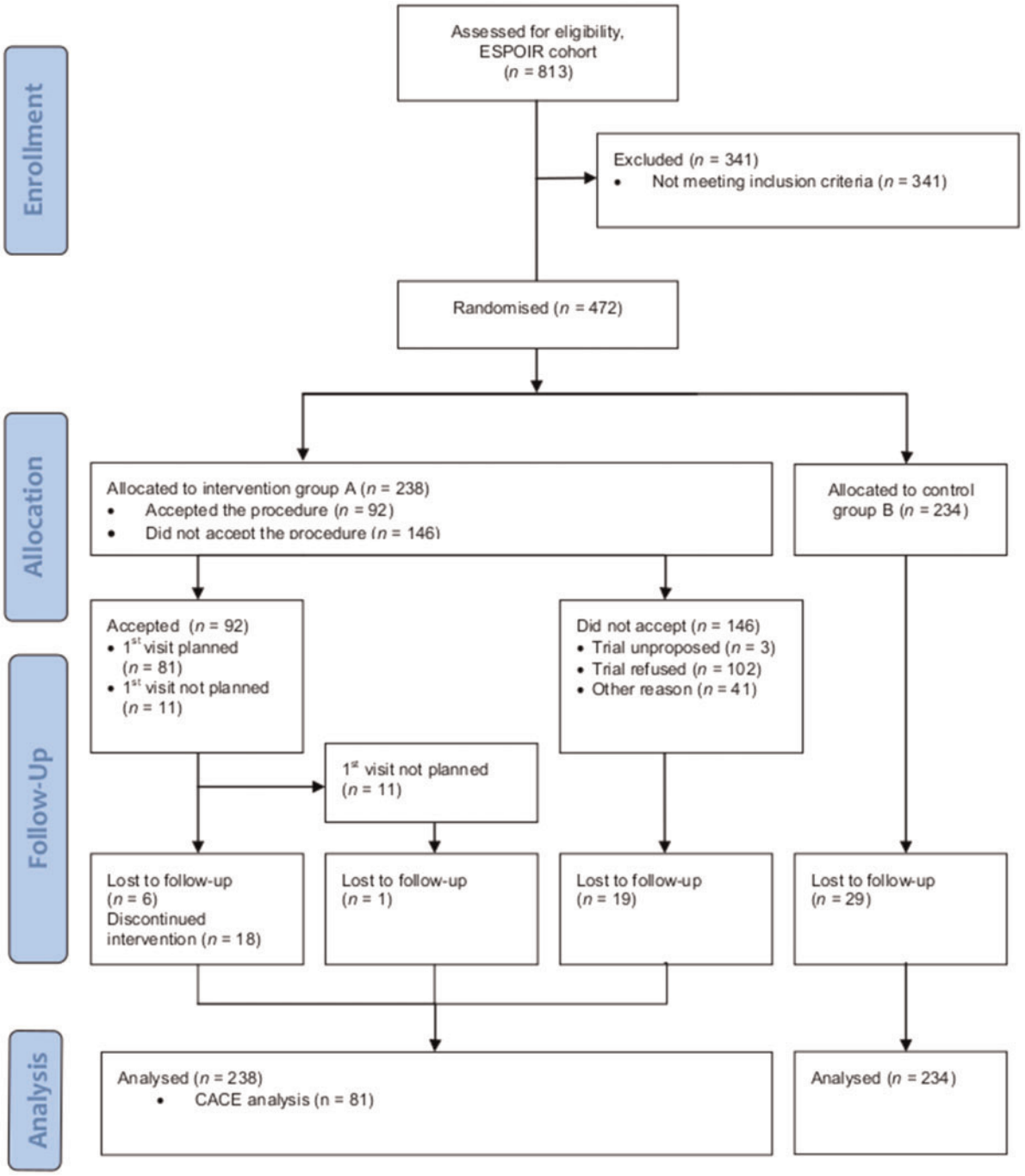
Duration of RA was 9.0 ± 0.7 years. Baseline DAS28-ESR was 2.7 ± 1.4 and 2.7 ± 1.3 in intervention and control groups, respectively. Ever smoking was present in 16.6% and 16% of patients, respectively. The percentage of patients with anti-CCP was 49.2% and 50.0%, respectively. Use of specific RA treatments was the same in both groups: methotrexate: 72.2% and 65.1% respectively; biologic treatment: 37.3% and 31.4% respectively; and prednisone: 21.9% and 20.2% respectively. Table 2A indicates that 56.2% of the patients had a periodontitis at baseline as defined by least two teeth with pocket depth > 4 mm. Patients with PD were more frequently anti-CCP+ (63% *vs* 53%) and had more active disease at baseline [mean DAS28-ESR 2.95 (S.D. 1.34) *vs* 2.18 (S.D. 1.22)].

Change in clinical activity of RA

The median duration between post and pre-randomization visits was 24 months (IQR: [24; 36]) for intervention group and 24 months (IQR: [24; 36]) for control group. Delta DAS28-ESR was −0.17 ± 1.29 and −0.09 ± 1.28 in intervention and control groups respectively (mean difference with CACE analysis: −0.37 (95% CI −1.12, 0.37) $P = 0.33$) (Fig. 2, Supplementary Tables S1A and S1B, available at *Rheumatology* online).

In anti-CCP positive patients, the delta DAS28-ESR was −0.12 ± 1.42 and 0.00 ± 1.37 in intervention and control groups, respectively (mean difference with CACE analysis: −0.43 (95% CI −1.37, 0.51), $P = 0.37$) (Fig. 2, Supplementary Tables S1A and 1B, available at *Rheumatology* online).

Fig. 1 Flow chart of the study



Patients lost to follow-up are patients for whom the post-randomization visit (collection of post-randomization DAS28-ESR) was not performed. All randomized patients are used to estimate the complier average causal effect.

Evaluation of the periodontal status

At baseline, detailed periodontal data were available in 73/81 patients who had a first visit to the dentist. Following the intervention, all the periodontal parameters were improved (Table 2A). Fifty-six percent of the patients had a periodontitis at baseline (41/73), whereas they were only 34% after 12 months (18/53). The mean percentage of bleeding sites decreased by 16% between baseline and 12 months, and the mean pocket depth decreased from 2.4 mm (S.D. 0.8) at

Table 1 Baseline characteristics of all randomized patients

Characteristics	Control group All, *n* = 234	Intervention group		
		All, *n* = 238	Refusals, *n* = 157	Acceptors, *n* = 81
RA duration (years), mean (S.D.)	9.0 (0.7)	9.0 (0.7)	9.0 (0.7)	8.9 (0.7)
Female sex, *n*/*N* (%)	178/234 (76.1)	192/238 (80.7)	127/157 (80.9)	65/81 (80.2)
Age (years), mean (S.D.)	58.1 (12.2)	57.7 (11.3)	58.8 (11.0)	55.6 (11.8)
Rheumatoid factor positive, *n*/*N* (%)	123/228 (53.9)	114/237 (48.1)	71/156 (45.5)	43/81 (53.0)
Anti-CCP positive, *n*/*N* (%)	117/234 (50.0)	117/238 (49.2)	71/157 (45.2)	46/81 (56.8)
DMARD, *n*/*N* (%)	169/234 (72.2)	169/238 (71.0)	109/157 (69.4)	60/81 (74.1)
Conventional DMARD, *n*/*N* (%)	149/169 (88.2)	155/169 (91.7)	101/109 (92.7)	54/60 (90.0)
Methotrexate, *n*/*N* (%)	110/169 (65.1)	122/169 (72.2)	76/109 (69.7)	46/60 (76.7)
Biologic DMARD, *n*/*N* (%)	53/169 (31.4)	63/169 (37.3)	37/109 (33.9)	26/60 (43.3)
Number of previous DMARD, mean (S.D.)	2.7 (3.3)	2.2 (2.6)	2.3 (2.9)	2.0 (2.0)
Corticosteroids, *n*/*N* (%)	47/233 (20.2)	52/237 (21.9)	37/156 (23.7)	15/81 (18.5)
If corticosteroids, dose (mg/d), mean (S.D.)	5.3 (2.9)	5.8 (4.6)	5.8 (5.0)	5.9 (3.7)
Tobacco, *n*/*N* (%)	38/229 (16.6)	38/237 (16.0)	27/156 (17.3)	11/81 (13.6)
Alcohol, *n*/*N* (%)	28/229 (12.2)	31/237 (13.1)	21/156 (13.4)	10/81 (12.3)
Xerostomia, *n*/*N* (%)	25/231 (10.8)	19/237 (8.0)	11/156 (7.1)	8/81 (9.9)
Number of swollen joints[a], mean (S.D.)	1.0 (2.2)	1.0 (2.1)	1.0 (2.2)	1.2 (2.0)
Number of tender joints[a], mean (S.D.)	2.5 (4.9)	2.6 (5.0)	2.7 (5.4)	2.3 (4.2)
DAS28-ESR[b], mean (S.D.)	2.7 (1.3)	2.7 (1.4)	2.7 (1.4)	2.7 (1.3)
HAQ[c], mean (S.D.)	0.5 (0.6)	0.6 (0.6)	0.6 (0.7)	0.5 (0.5)
ESR[d] (mm), mean (S.D.)	15.7 (15.5)	13.9 (11.4)	14.4 (11.4)	13.0 (11.4)
CRP[e] (mg/l), mean (S.D.)	6.5 (13.3)	5.0 (5.5)	5.4 (6.3)	4.2 (3.5)

[a]6 missing data, 4 in control, 2 in intervention, 2 in refusals, 0 in acceptors. [b]30 missing data, 17 in control, 13 in intervention, 12 in refusals, 1 in acceptors. [c]4 missing data, 2 in control, 2 in intervention, 2 in refusals, 0 in acceptors. [d]26 missing data, 15 in control, 11 in intervention, 10 in refusals, 1 in acceptors. [e]22 missing data, 14 in control, 8 in intervention, 7 in refusals, 1 in acceptors. IQR: interquartile range; DAS28-ESR, DAS in 28 joints-ESR.

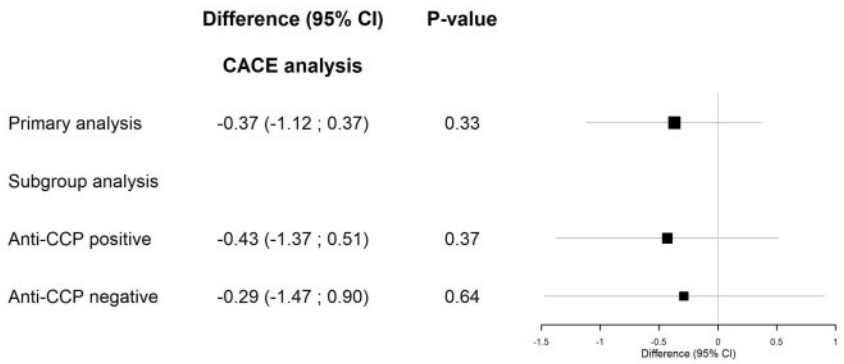
Table 2A Periodontal characteristics changes in the patients who had their first visit to the dentist (*n* = 81)

Characteristics	M0	*n*	M6	*n*	M12	*n*
Number of teeth (/28), mean (S.D.)	23.6 (5.3)	73	23.3 (5.6)	52	22.8 (5.8)	50
Site with plaque (%), mean (S.D.)	29.9 (25.1)	72	20.7 (22.9)	52	16.1 (20.8)	52
Bleeding on probing (%), mean (S.D.)	30.5 (29.5)	72	20.4 (25.0)	50	14.5 (14.9)	49
Pocket depth (mm), mean (S.D.)	2.4 (0.8)	73	2.2 (0.7)	53	2.1 (0.7)	53
Pocket depth $\geqslant$6 mm (%), mean (S.D.)	2.4 (4.8)	73	1.9 (4.7)	53	1.3 (4.2)	53
Clinical attachment loss $\geqslant$ 4 mm (%), mean (S.D.)	27.3 (26.2)	69	23.6 (26.6)	48	24.4 (27.3)	48
Patient with at least two teeth with pocket depth $>$ 4 mm, *n* (%)	41 (56.2)	73	22 (41.5)	53	18 (34.0)	53

Table 2B Periodontal characteristics changes in the patients who had their three visits to the dentist (*n* = 50)

Characteristic	M0	*n*	M6	*n*	M12	*n*
Number of teeth (/28), mean (S.D.)	23.5 (5.5)	49	23.1 (5.8)	47	22.4 (6.1)	44
Site with plaque (%), mean (S.D.)	27.1 (25.7)	48	19.1 (23.0)	46	16.6 (21.8)	46
Bleeding on probing (%), mean (S.D.)	25.1 (26.4)	48	18.6 (22.9)	44	15.2 (15.7)	43
Pocket depth (mm), mean (S.D.)	2.4 (0.9)	49	2.2 (0.7)	47	2.1 (0.7)	47
Pocket depth $\geqslant$ 6 mm (%), mean (S.D.)	2.6 (5.4)	49	2.0 (5.0)	47	1.3 (4.4)	47
Clinical attachment loss $\geqslant$ 4 mm (%), mean (S.D.)	27.2 (27.7)	46	25.0 (27.6)	42	24.8 (28.9)	42
Patient with at least two teeth with pocket depth $>$ 4 mm, *n* (%)	27 (55.1)	49	20 (42.6)	47	15 (31.9)	47

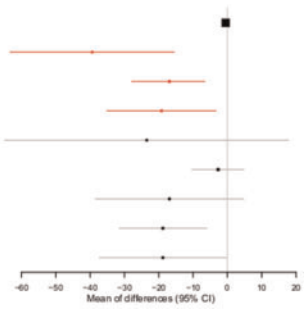
Fig. 2 Treatment effect (difference of delta DAS28-ESR) for primary and subgroup analyses (imputed data)



CACE: complier average causal effect.

Fig. 3 Mean change of bacterial load (total number of bacterias) (×106) for the nine bacteria

	M0 mean (sd)	M12 mean (sd)	Mean of differences (95%CI)
Aggregatibacter actinomycetemcomitans	1.1 (4.8)	0.6 (3.7)	−0.5 (−1.6 to 0.6)
Porphyromonas gingivalis	54.1 (117.0)	14.7 (51.6)	−39.4 (−63.3 to −15.5)
Tannerella forsythia	19.5 (35.7)	2.6 (5.8)	−16.9 (−27.9 to −6.6)
Treponema denticola	24.6 (54.7)	5.4 (12.2)	−19.2 (−35.1 to −3.3)
Prevotella intermedia	54.3 (80.4)	30.7 (120.1)	−23.5 (−64.9 to 17.8)
Peptostreptococcus micros	12.2 (21.2)	9.5 (21.5)	−2.7 (−10.3 to 4.8)
Fusobacterium nucleatum	38.7 (69.9)	21.9 (42.3)	−16.9 (−38.5 to 4.8)
Campylobacter rectus	28.4 (45.2)	9.6 (17.7)	−18.8 (−31.5 to −6.0)
Eikenella corrodens	20.1 (63.1)	1.4 (2.5)	−18.8 (−37.3 to −0.2)



Results are given for the 47 patients who had their bacterial load collected before and after the intervention.

baseline to 2.1 mm (s.d. 0.7) at 12 months. Interestingly, the same trend was observed with the compliant patients that underwent the three visits (baseline, 6-month and 12-month) (Table 2B).

Evaluation of PD-associated bacterial load

Change in bacterial load (total number of bacteria) could be assessed at baseline in 75 patients and at follow-up in 47 patients from the intervention group. Microbiological analysis of the periodontal bacteria indicated a significant decrease in the red complex involved in the pathogenesis of periodontitis, i.e. *Porphyromonas gingivalis* (mean change -39.4×10^6 (95% C: −63.3, −15.5), $P = 0.002$), *Tannerella forsythia* (mean change -16.9×10^6 (95% CI −35.1, −6.6), $P = 0.002$) and *Treponema denticola* (mean change -19.2×10^6 (95% CI −35.1, −3.3), $P = 0.019$). Of note, the bacterial load of *Campylobacter rectus* was also significantly decreased after the intervention (mean change -18.8×10^6 (95% CI −31.5, −6), $P = 0.005$). The mean change of the nine bacterial loads is presented in Fig. 3.

Change in clinical activity of RA in sub-groups of patients with PD

In the intervention group, the 41 patients with PD had a slightly more important decrease of DAS28-ESR than the 32 patients without PD: −0.45 (1.33) *vs* 0.24 (1.12), respectively (Table 3A).

In the intervention group, the 42 patients with pathogenic bacterial load (defined by the presence of at least one bacterium of the red complex) had a slightly more important decrease of DAS28-ESR than the 33 patients without pathogenic bacterial load: −0.31 (1.39) *vs* 0.00 (1.20), respectively (Table 3B).

In the intervention group, the 23 patients initially positive and who became PCR negative for one of the three bacteria of the red complex, had a slightly more important decrease of DAS28-ESR than the 24 patients presenting

Table 3A Baseline characteristics and treatment effect in the patients with and without periodontal disease (imputed data)

	Periodontal disease, *n* = 41	No periodontal disease, *n* = 32
Anti-CCP positive, *n*/*N* (%)	26/41 (63.4)	17/32 (53.1)
DAS28-ESR pre-randomization, mean (S.D.)	2.92 (1.34)	2.18 (1.22)
DAS28-ESR post-randomization, mean (S.D.)	2.47 (1.37)	2.42 (1.21)
Delta DAS28-ESR (post–pre), mean (S.D.)	−0.45 (1.33)	0.24 (1.12)

DAS28-ESR: DAS in 28 joints-ESR.

Table 3B Baseline characteristics and treatment effect in patients with and without pathogenic bacterial load (imputed data)

	Pathogenic bacterial load, *n* = 42	No pathogenic bacterial load, *n* = 33
Anti-CCP positive, *n*/*N* (%)	21/42 (50.0)	23/33 (69.7)
DAS28-ESR pre-randomization, mean (S.D.)	2.78 (1.29)	2.43 (1.23)
DAS28-ESR post-randomization, mean (S.D.)	2.47 (1.26)	2.43 (1.22)
Delta DAS28-ESR (post–pre), mean (S.D.)	−0.31 (1.39)	0.00 (1.20)

DAS28-ESR: DAS in 28 joints-ESR.

Table 3C Baseline characteristics and treatment effect in patients becoming negative for the red complex (imputed data)

	Initially positive who became PCR negative for one of the three bacteria of the red complex, *n* = 23	Other evolution, *n* = 24
Anti-CCP positive, *n*/*N* (%)	14/23 (60.9)	14/24 (58.3)
DAS28-ESR pre-randomization, mean (S.D.)	2.86 (1.47)	2.39 (0.98)
DAS28-ESR post-randomization, mean (S.D.)	2.42 (1.51)	2.25 (1.16)
Delta DAS28-ESR (post–pre), mean (S.D.)	−0.44 (1.51)	−0.14 (1.13)

another evolution: −0.44 (1.51) *vs* −0.14 (1.13), respectively (Table 3C).

Discussion

This randomized study nested in the ESPOIR cohort demonstrated that in RA patients, the recommendations to the general population for good oral hygiene decreased the bacterial load of bacteria involved in PD but did not improve RA activity. In anti-CCP positive patients, the intervention was not effective either on RA clinical activity. In patients with PD at baseline and in those who became PCR negative for one of the three bacteria of the red complex if initially positive at baseline, there was a slightly more important decrease of DAS28-ESR.

Numbers of factors may explain the lack of clinical effect on RA. Firstly, because we proposed a preventive treatment recommended in the general population, we did not require PD as an inclusion criterion and effectively almost half of our RA patients in the intervention group did not have PD. However, the rate of PD was slightly higher than the prevalence of PD in the general population of industrialized countries [23]. Interestingly, the rate of PD decreased after the intervention from 56% to 34%, but one-third of the patients still had PD. Thus, there is no doubt that oral hygiene was not sufficient for these patients, and that addition periodontal therapy was mandatory. Secondly, even if ESPOIR is a cohort of patients with early arthritis at inclusion, the mean duration of arthritis at inclusion in BHYRRA was almost 10 years. If PD may induce or influence activity of RA, it is probably before the first clinical signs of RA or at its beginning. Thirdly and mainly, the patients included in BHYRRA had a very good control of their disease at baseline (DAS28-ESR around 2.7, very close to the threshold of remission), continued their DMARD and it might be difficult to improve them further. Unfortunately, we did not have access to other

activity scores such as Clinical DAS or Simplified Disease Activity Score, but it is improbable that their changes would have been different from that of the DAS28-ESR. Lastly, the compliance of tooth brushing and mouthwash was not monitored in the intervention group and the percentage of patients of the control group who performed good oral hygiene on their own was not known.

One strength of our study is that it involved real-life patients. We demonstrate the feasibility of conducting a randomized trial nested in existing cohorts. Because it is more and more difficult to include patients in clinical trials, this approach could be used in a number of existing cohorts in rheumatology for testing new ways of managing patients [24].

The other strength of our study is its completely randomized design and the high number of patients included. In the others studies of the literature having evaluated if non-surgical treatment of PD could improve clinical activity of RA (five of them shared in a recent meta-analysis [25] and two more recent ones [26–27]), the number of treated patients was always <30 and the choice of the control group was not always done by a strict randomization. Nevertheless, individually, five out of these six studies showed a reduction in DAS28 score following non-surgical treatment of PD, but this effect was not found statistically significant in the recently published meta-analysis sharing four of them [25]. An important difference between these previous studies and ours is that all recruited patients had RA and PD and that baseline activity of RA was more important.

In the context of our study that was more preventive than curative, because we proposed an intervention based on general recommendations to the general population over 50 years, it is remarkable to observe that this preventive treatment was really effective in decreasing the bacterial load. Moreover, patients with PD at baseline and patients who became PCR negative for one of the three bacteria of the red complex if initially positive at baseline had a numerically higher decrease of DAS28-ESR higher compared with the other treated patients. Interestingly, at baseline, patients with PD had a numerically higher DAS28 and an increased frequency of anti-CCP positivity than patients without PD. A recent study also showed higher frequency of anti-CCP but no higher DAS28 in RA patients with PD [28].

Lastly, in the current debate on the impact of periodontal pathogens in the association of RA and PD, it is interesting to note that *Aa* and *Pg* were detected at baseline in 3/75 and 49/75 patients, respectively. The low rate of *Aa* is in accordance with other studies in adults [29]. Other bacteria of the red complex, *Tannerella forsythia* and *Treponema denticola* were present at baseline in 68/75 and 53/75 patients, respectively. The bacterial load of these three bacteria of the red complex significantly decreased after 12 months, which is remarkable with a preventive intervention dedicated to the general population.

In conclusion, these simple recommendations of good oral hygiene in RA patients were able to decrease the bacterial load of bacteria involved in PD and should be tested in patients with earlier RA, more active disease and probably some signs of PD.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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