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Original article

The effect of periodontal treatment on patients with rheumatoid arthritis: The ESPERA randomised controlled trial

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ABSTRACT

Objectives: To assess the effect of periodontal treatment on clinical and biochemical parameters of rheumatoid arthritis (RA) and quality of life (QoL) in patients with moderately active RA who were diagnosed with periodontitis.

Methods: In this open-label randomised controlled trial, RA subjects ($n=22$) were allocated to "immediate" or "delayed" periodontal treatment (full-mouth non-surgical scaling and root planing, systemic antibiotics, and oral hygiene instructions). The main outcome was the 3-month change on the Disease Activity Score 28 based on the Erythrocyte Sedimentation Rate (DAS28-ESR). The Health Assessment Questionnaire and the General Oral Health Assessment Index were used to assess general and oral health QoL, respectively.

Results: Periodontal health significantly improved after periodontal treatment ($P=0.03$). Periodontal treatment appeared to be safe but led to no significant effects on the DAS28-ESR (adjusted mean difference with 95% confidence interval (aMD) of −0.03 [−0.98; 0.92]). There was no evidence of improvement in the general QoL after periodontal treatment and no significant effect was found for the oral health QoL, despite a positive trend in the "psychological impacts" domain (aMD of 0.13 [−0.07; 0.33], $P=0.20$).

Conclusions: Although no clinical effect of periodontal treatment on RA was identified, this trial provides important data to support periodontal care in RA patients. Periodontal treatment is safe and reduces oral inflammation with a possible effect on oral health QoL. Since both periodontitis and RA are complex and multifactorial chronic diseases, it is likely that patient-centred approaches involving both oral health professionals and rheumatologists will contribute to optimal patient care. ISRCTN79186420.

1. Introduction

Periodontitis is the most prevalent chronic immune/infectious disease and the global prevalence of severe periodontitis is estimated at 10% [1]. This disease is characterised by the loss of tooth-supporting tissues [1]. If left untreated, periodontitis can result in tooth loss with a significant negative impact on oral

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health and overall quality of life [2]. Dozens of systemic diseases have been believed to be associated with periodontitis [3] and the potential link between rheumatoid arthritis (RA) and periodontitis has been brought to light over the past decades [3]. RA is a chronic autoimmune disease with a prevalence of 0.5% to 1% in Europe and North America (overall prevalence of 0.31% in France), characterised by progressive articular destruction and associated with several comorbidities and a subsequent decline in quality of life [4]. Although the underlying mechanisms are not fully understood, the characteristics and pathogenic processes of RA mirror those of periodontitis, and evidence supports the notion of a bidirectional relationship. RA and periodontitis have the same genetic susceptibility and contributing environmental factors, including some HLA genotypes, smoking, socioeconomic status, lifestyle and stress [5,6]. It has also been suggested that the oral microbiome (periopathogens *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*) promotes and/or worsens RA by affecting tissue protein citrullination. Periodontal therapy may help to reduce local inflammation and bacterial load, which in turn reduces the putative systemic entry of pro-inflammatory molecules (e.g. TNFα, IL-1, IL-17) and bacterial by-products or enzymes (e.g. lipopolysaccharides from gram negative bacterial walls, peptidylarginine deiminases [5,6]).

Clinical trials on this subject suggest a positive effect of periodontal treatment on biological and clinical measures for RA [7–10]. However, a 2014 systematic review and meta-analysis drew attention to the fact that some methodological aspects should be improved in future trials. In particular, there is a need for a better-controlled intervention and more rigorous clinical and biochemical measurements [11]. In addition, more emphasis should be given to patient-centred outcomes such as quality of life parameters. The oral health-related quality of life (OHRQoL) has be shown to be highly affected in RA patients [12,13].

The main objective of this randomised trial was to assess the effect of periodontal treatment on clinical and biological parameters of rheumatoid arthritis in patients also diagnosed with periodontitis. Secondary objectives were to determine the effect of periodontal treatment on periodontal health and quality of life and whether it is safe in this context.

2. Methods

The full study protocol was published [14] and registered before the first participants were enrolled (ISRCTN79186420). This study followed the CONSORT guidelines [Appendix A, Table S1; See the supplementary material associated with this article online].

2.1. Trial design, setting and ethics

The ESPERA (Experimental Study of Periodontitis and Rheumatoid Arthritis) trial is a prospective, open-label, randomised controlled clinical study. This is a two-centre trial with two parallel groups ("immediate" periodontal treatment for the treatment group versus "delayed" periodontal treatment for the control group, with a balanced 1:1 treatment allocation) and follow-up of three months.

The trial was conducted in accordance with the provisions of the Declaration of Helsinki and French Good Clinical Practice guidelines. All participants gave their written informed consent. The trial was approved by an independent ethics committee (ID-RCB-2010-A00533-36, CPP Sud-Ouest Outremer 1 on 11-JUL-2011) and regulatory agencies (AFSSAPS No.2010-A01193-36 on 04-NOV-2010).

2.2. Participants

The patients were recruited between 06 March 2012 and 15 June 2015 in the Rheumatology Departments of two teaching hospitals in southwestern France (Toulouse-Purpan and Bordeaux-Pellegrin). Subjects were included if: they had been diagnosed with RA at least one year before the date of inclusion (according to the 1987 revised American Rheumatism Association criteria for the classification of RA); their RA was moderately active on the date of inclusion (Disease Activity Score 28 using the Erythrocyte Sedimentation Rate, i.e., DAS28-ESR score between 3.2 and 5.1); and their RA treatment was unchanged over the previous three months (no change in dosage, formulation or method of administration). To be included, patients needed to have at least six permanent natural teeth and a diagnosis of periodontitis attested by the presence of at least four teeth with at least one probed site with a clinical attachment loss (CAL) $\geq$ 3 mm and periodontal pocket depth (PPD) $\geq$ 4 mm [15].

2.3. Study intervention

Periodontal treatment was administered over the ten days following the inclusion visit for the immediate treatment group, and at the end of the 3-month follow-up period for the delayed control group (Appendix A, Fig. S1), for ethical reasons. Periodontal treatment included full-mouth disinfection with non-surgical scaling and root planing (SRP), systemic antibiotics (amoxicillin 1.5 g/day or, in case of allergy to this molecule, 1200 mg clindamycin, for seven days after periodontal treatment), and oral hygiene instructions. Briefly, SRP was performed during a single, 2-hour, full-mouth ultrasonic and hand instrument debridement session by dental surgeons who had received special training from an experienced periodontist prior to the launch of the study. SRP was combined with subgingival irrigation with an antiseptic mouth rinse (chlorhexidine 0.12%). After SRP, subjects received personalised oral hygiene instructions, antibiotics and a free pack containing all the dental care products needed for three months of periodontal maintenance.

2.4. Primary outcome assessment

The primary outcome of the ESPERA trial was the change in RA activity, measured by the DAS28-ESR between the inclusion visit (V1) and the 3-month follow-up visit (V4 endpoint). The DAS28-ESR was computed from the number of tender and swollen joints (out of the 28 evaluated joints), the ESR in one hour, and the patient's overall assessment of their health (0 to 100).

2.5. Secondary outcomes

RA activity improvement was also evaluated using the American College of Rheumatology 20%, 50% and 70% improvement criteria (ACR 20, 50 and 70) [16]. For example, ACR 20 corresponds to a 20% improvement in the number of tender or swollen joints as well as a 20% improvement in at least three of the five other criteria: patient's overall health assessment, physician's assessment, pain scale, disability/functional questionnaire and acute phase reactant (ESR or CRP).

The change in RA disability (Health Related QoL - HRQoL) was measured by the Health Assessment Questionnaire (HAQ) between V1 and V4. Each of the eight subdomains (dressing, rising, eating, walking, hygiene, reach, grip and activity) were also considered. The scores for each domain were grouped and calculated with a mean global score between 0, indicating full ability to perform the activities, and 3, indicating total incapacity [17]. Another patient-centred outcome was based on the General Oral Health

Assessment Index (GOHAI), a self-administered questionnaire validated in French [18,19] to study the OHRQoL. The GOHAI contains 12 items that assess physical functioning, pain and discomfort and psychosocial impacts. The scores for the answers were re-coded when necessary so that responses that indicate good conditions and no problems had the highest scores. GOHAI was analysed as an additive score (Add-GOHAI) and included the three dimensions [12]. For a better evaluation, these scores were expressed as percentages. The safety and efficacy of periodontal treatment on the periodontal health of RA patients were also considered. All adverse health events during the 3-month follow-up period were recorded for both groups after each participant was interviewed. Special emphasis was placed on reporting any potential adverse oral health events.

2.6. Data collection

Clinical investigators collected sociodemographic data, medical history and treatment, RA outcomes, QoL outcomes and oral hygiene habits. RA outcomes were measured by rheumatologists who were blinded to the subjects' group assignment. Full-mouth periodontal charting included CAL, PPD and bleeding on probing (BoP). Initial periodontal charting was performed before randomisation, using a constant pressure probe (Florida Probe®; Gainesville, FL, USA) with six measurements per tooth [20] at inclusion and after months. Moreover, investigators were trained before the launch of the study (overall inter-examiner kappa was as high as 0.9 for CAL, PPD and BoP). Periodontal investigators could not be blinded to the subjects' group assignment during follow-up visits. Using the individual periodontal measurements, the total periodontal inflammatory burden was also estimated at the participant level, taking into account periodontitis severity, extent and activity. The total gingival epithelium surface (Periodontal Epithelial Surface Area – PESA) and the total surface area of inflamed gingiva (Periodontal Inflammation Surface Area – PISA) were also calculated [21] and periodontitis was classified at baseline according to the extent and severity [22]. Severity was based on the CAL: mild (mean of 1–2 mm periodontal attachment loss), moderate (mean of 3–4 mm periodontal attachment loss) or severe (mean $\geq$ 5 mm periodontal attachment loss). Extent was characterised as localised ($\leq$ 30% of sites involved) or generalised (> 30%).

2.7. Statistical analyses

Sample size calculation was based on detecting a 0.6 point change in DAS28-ESR from baseline in the two groups; 0.6 was chosen because it is the minimum therapeutic response according to EULAR [23]. Assuming a standard deviation of 0.6 [9], a two-sided test at a 5% significance level with 16 participants per group would yield an 80% power. In anticipation of a 25% drop out rate, the initial target sample size was 40 participants (20 per centre, with independent randomisation between the two centres). The random allocation sequence was generated using a computer number generator to select random permuted blocks (block lengths of 2, 4, 6 and 8), stratified by clinical centre. Randomisation cards were printed and sealed in sequentially numbered, opaque envelopes by an independent research assistant prior to the beginning of the trial [14].

The analysis was performed as an intention to treat; the changes in DAS28-ESR during the follow-up period were compared between the two arms. The mean differences were estimated with their 95% confidence intervals and were analysed using an analysis of covariance (ANCOVA) model, adjusted for the baseline DAS28-ESR level and the clinical centre (aMD). Residual values were tested for an approximated normal distribution. To assess the efficacy of periodontal treatment in periodontal health and other secondary outcomes, variables were also analysed using an ANCOVA model adjusted for the baseline level of the variable and the clinical centre. The proportion of subjects who had one or more adverse event in the two groups was compared using Fisher's Exact test. The level of statistical significance was set at 5% ($P < 0.05$).

3. Results

3.1. Participants

A total of 139 individuals were screened, particularly because these subjects presented adequate RA inclusion criteria during their previous rheumatology appointment. Nevertheless, 117 were not included: 31 subjects declined to participate, and 86 subjects did not meet inclusion criteria for oral or rheumatological reasons (Fig. 1). A total of 22 participants were randomised (Fig. 1, Table 1). The management of RA according to tight control, treat-to-target strategies may explain the difficulty of recruitment with frequent changes in therapeutics if the patient remained in an active disease state. Additionally, an interim analysis demonstrated a low conditional power (threshold below 35%) and an effect size very close to a null effect (mean difference close to zero, Table 2). The trial's scientific committee therefore decided to end recruitment due to futility reasons [24]. The control and treatment groups consisted of 11 subjects each.

3.2. The effect of periodontal treatment on clinical and biological parameters of RA

No statistically significant differences in DAS28-ESR were found between the groups (Table 2, Fig. 2a). The ANCOVA, adjusted on the baseline value and clinical centre, also showed no difference between the two groups (aMD −0.03 [−0.98; 0.92], $P = 0.95$). No difference was detected for the components of the DAS28-ESR, C-Reactive Protein level or the binary ACR 20, 50 and 70 outcomes.

3.3. Evidence of improved periodontal health after periodontal treatment

One patient in the control group and two patients in the treatment group refused to undergo the final periodontal examination. Patients were anxious about the potential triggering of an RA crisis. Mean PPD, mean CAL and % BoP sites improved three months after SRP (adjusted mean difference with a 95% confidence interval (aMD) of −0.17 mm [−0.37; 0.03], −0.17 mm [−< 0.53; 0.18] and −11.8% [−24.7; 0.01], respectively, although this improvement was not statistically significant. The mean PESA and PISA significantly decreased after periodontal treatment (aMD of −127.7 mm^2 [−246.5; −8.9] and −91.8 mm^2 [−172.2; −11.3], respectively) (Table 3, Fig. 2b).

3.4. Periodontal treatment does not improve quality of life

No significant effect was found for the OHRQoL, despite a positive trend in the "psychological impacts" domain (aMD 0.13 [−0.07; 0.33], $P = 0.20$; Table 4). No effect was found for the HAQ or any of the subdomains (Table 4).

3.5. Safety of periodontal treatment

During the 3-month follow-up visit, six subjects in the control group and eight subjects in the treatment group reported having been hospitalised or having had a health problem that might affect the course of the clinical trial ($P = 0.22$). Six control subjects

Table 1
Sociodemographic and medical characteristics of the subjects at inclusion.

Sociodemographic characteristics	*n*	Control group	*n*	Treatment group	*P*[b]
Age (years)	11	58.5 ± 8.7	11	64.7 ± 5.7	0.14
Women	11	8 (73%)	11	6 (55%)	0.66
Level of education					
Elementary school	11	3 (27%)	10	1 (10%)	0.07
Middle school		5 (45%)		2 (20%)	
High school		3 (27%)		2 (20%)	
University level		0 (0%)		5 (50%)	
Professional activities					
Farmers, operators: primary sector	11	0 (0%)	11	0 (0%)	0.28
Artisans, traders and entrepreneurs		2 (18%)		1 (9%)	
Executives, intellectual professions		0 (0%)		0 (0%)	
Intermediate occupations		0 (0%)		0 (0%)	
Blue-collar employees, workers		3 (27%)		0 (0%)	
Retirees		5 (45%)		9 (82%)	
Other people without work		1 (9%)		1 (9%)	
Native country					
France	11	10 (91%)	11	11 (100%)	> 0.99
Other		1 (9%)		0 (0%)	
[10pt] Medical characteristics	*n*	Control group	*n*	Treatment group	*P*[b]
Body mass index (kg/m^2)	11	29.3 ± 9.2	9	26.4 ± 4.4	0.65
Smokers	11	4 (36%)	10	4 (40%)	> 0.99
Duration of smoking (years)	4	30.8 ± 23.4	4	27.5 ± 15.0	0.82
Number of cigarettes a day	4	11.3 ± 4.8	4	7.5 ± 2.9	0.23
Drug treatments (except primary treatment for RA)[a]					
Digestive system and metabolism	11	7 (64%)	10	5 (50%)	0.67
Blood and blood-forming organs		8 (73%)		8 (80%)	> 0.99
Cardiovascular system		6 (55%)		7 (70%)	> 0.99
Dermatology		0 (0%)		1 (10%)	> 0.99
Urogenital system		1 (9%)		1 (10%)	> 0.99
Systemic hormones		2 (18%)		0 (0%)	0.48
Systemic anti-infective		2 (18%)		0 (0%)	0.48
Musculoskeletal system		4 (36%)		1 (10%)	0.31
Nervous system		6 (55%)		4 (40%)	0.67
Respiratory tract system		3 (27%)		0 (0%)	0.21
Sensory organs		0 (0%)		1 (10%)	> 0.99
RA ACPA positive	11	8 (73%)	11	10 (91%)	0.59
RA duration (years)	11	11.4 ± 8.6	11	12.1 ± 6.5	0.62
Last modification of treatment (years)	8	3.3 ± 5.1	10	1.8 ± 3.1	0.48
Severe RA (HAQ > 0.5)	11	9 (82%)	10	9 (90%)	> 0.99
Type of RA therapy					
csDMARDs	11	9 (82%)	11	8 (73%)	> 0.99
bDMARDs		10 (91%)		7 (64%)	0.31
Glucocorticoids		5 (45%)		6 (55%)	> 0.99
NSAIDs		4 (36%)		4 (36%)	> 0.99
[10pt] Dental characteristics	*n*	Control group	*n*	Treatment group	*P*[b]
Last visit to the dentist (months)	11	1.6 ± 2.4	9	2.3 ± 3.5	0.59
Brushing frequency					
At least twice a day	11	7 (64%)	10	6 (60%)	> 0.99
Once a day		3 (27%)		2 (20%)	
Sporadically or never		1 (9%)		2 (20%)	
Interproximal hygiene frequency					
Once a day	11	1 (9%)	10	1 (10%)	> 0.99
Every week		0 (0%)		0 (0%)	
Sporadically or never		10 (91%)		9 (90%)	
Mouthwash use frequency					
Once a day	11	1 (9%)	10	0 (0%)	0.49
Every week		2 (18%)		4 (40%)	
Sporadically or never		8 (73%)		6 (60%)	
Frequency of visit to the dentist					
At least twice a year	11	3 (27%)	9	1 (11%)	0.93
Once a year		3 (27%)		2 (22%)	
Once every two years		2 (18%)		2 (22%)	
Less than once every two years		3 (27%)		4 (44%)	
Previously informed about the importance of oral health in RA patients	11	1 (9%)	10	1 (10%)	> 0.99
Periodontitis extent and severity					
Generalised severe	11	1 (9%)	11	3 (27%)	0.31
Generalised moderate		3 (27%)		3 (27%)	> 0.99

Table 1 (*Continued*)

Dental characteristics	*n*	Control group	*n*	Treatment group	*P*[b]
Localised severe		6 (55%)		4 (36%)	0.67
Localised moderate		1 (9%)		1 (9%)	>0.99
Number of missing teeth	11	10.8 ± 6.0	10	12.0 ± 7.5	0.72

Results are presented as mean ± standard deviation for quantitative outcomes and as frequency (%) for qualitative outcomes.
ACPA: anti-citrullinated protein antibody; bDMARD: biological DMARDs; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; NSAID: non-steroidal anti-inflammatory drugs; RA: rheumatoid arthritis.

[a] Drug treatments were classified using the Anatomical Therapeutic Chemical (ATC) classification.

[b] *P*-value of the non-parametric Mann–Whitney or exact Fisher's test for a difference between control and treatment groups.

and three treatment group subjects experienced oral disorders ($P = 0.25$).

4. Discussion

In this 3-month randomised controlled clinical trial, periodontal treatment had no effect on disease activity in patients with active rheumatoid arthritis. Although other clinical trials on this subject have been published in recent years [11], our study provides new and important information.

First, although the final sample size is fairly small and therefore underpowered, this study gathered a wide range of clinical and biological data. These results will fuel future meta-analyses.

Second, this trial is consistent with current evidence that the effect of periodontal treatment on systemic diseases is, at best, clinically modest, as it was recently demonstrated for diabetes in a large-scale clinical trial and confirmed by the decrease in effect sizes in a recent Cochrane systematic review [25,26]. In this study, the care given to the randomisation process and the subsequent formation of the control group with methodological rigor may also explain the "negative results" we obtained [11,14]. Despite the fact that our control group was a true "no periodontal treatment" control arm, there was no loss of opportunity for the participants. In fact, the 3-month delay between the diagnosis of periodontitis and the treatment in our trial corresponded with the average waiting time for the treatment of chronic periodontitis in our routine hospital practice. Futility cannot be explained by ineffective periodontal treatment since periodontal health significantly improved after periodontal treatment (periodontal inflammation significantly diminished in the intervention group). Furthermore, the addition of antibiotics to the periodontal treatment argues in favour of optimal non-surgical periodontal treatment. The statistically insignificant improvement in PPD and CAL can be blamed on the lack of final power in the study. Nevertheless, the levels of periodontal improvements (PPD improvements of 0.3–0.4 mm) are consistent with other clinical studies [7–10].

The ESPERA participants had an initial mean PPD of approximately 2.3 mm and 13% BoP. Periodontal conditions are different from the 3 mm PPD and 20–50% BoP in other clinical trials [7–10]. This particularly low level of BoP might be explained by the fact

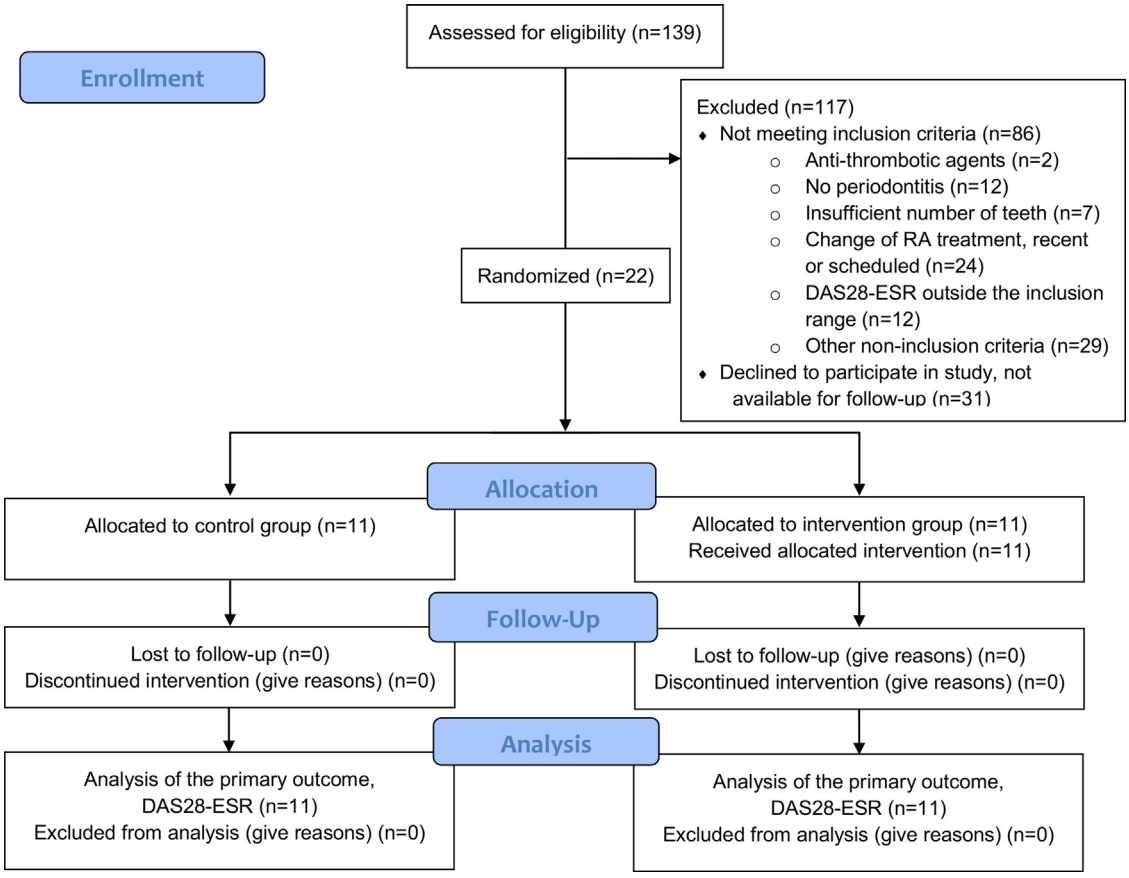

Fig. 1. Flow diagram for the study, according to the CONSORT statements.

Table 2
Effect of the intervention on clinical and biological markers related to rheumatoid arthritis.

Medical outcomes	*n*	Control group Mean ± SD	*n*	Treatment group Mean ± SD	*P*[a]	Adjusted mean difference[b] aMD [CI95%]	*P*[c]
Tender joints (0–28)							
V1	11	5.09 ± 4.35	11	6.27 ± 3.95	0.43	1.94 [−2.34; 6.23]	0.35
V4	11	3.55 ± 3.30	11	6.27 ± 6.59	0.49		
Swollen joints (0–28)							
V1	11	1.55 ± 2.07	11	2.82 ± 2.27	0.07	0.85 [−0.96; 2.65]	0.34
V4	11	0.82 ± 0.98	11	2.36 ± 2.98	0.33		
Erythrocyte Sedimentation Rate (1-hour ESR, mm. h^{-1})							
V1	11	20.55 ± 14.87	11	21.73 ± 14.89	0.77	2.30 [−12.77; 17.38]	0.75
V4	11	21.45 ± 14.29	11	24.00 ± 18.25	0.90		
C-Reactive Protein (CRP, mg. L^{-1})							
V1	11	6.45 ± 3.34	10	10.61 ± 7.03	0.13	1.68 [−4.39; 7.75]	0.57
V4	11	7.42 ± 3.61	11	12.23 ± 10.37	0.51		
Patient's overall assessment (0–100)							
V1	11	40.91 ± 23.43	11	32.91 ± 16.62	0.43	6.25 [−7.20; 19.70]	0.34
V4	11	30.27 ± 21.51	11	30.45 ± 22.19	0.95		
Physician's overall assessment (0–100)							
V1	11	28.18 ± 18.88	11	35.36 ± 15.76	0.23	-4.34 [−22.23; 13.56]	0.62
V4	11	30.00 ± 20.98	11	30.45 ± 22.19	0.95		
Pain scale (0–100)							
V1	11	40.91 ± 23.43	11	33.82 ± 17.30	0.49	4.00 [−10.48; 18.47]	0.57
V4	11	31.82 ± 20.89	11	31.36 ± 21.92	1.00		
Disease Activity Score 28 (DAS28-ESR)							
V1	11	3.82 ± 0.54	11	4.24 ± 0.61	0.12	−0.03 [−0.98; 0.92]	0.95
V4	11	3.47 ± 0.93	11	3.96 ± 1.40	0.22		
American College of Rheumatology - ACR20	11	7 (64%)	11	4 (36%)	0.20	–	–
ACR50	11	3 (27%)	11	3 (27%)	0.68	–	–
ACR70	11	2 (18%)	11	2 (18%)	0.71	–	–

Results are presented as mean ± standard deviation (SD) for the first visit (V1) and the visit in three months (V4).
[a] *P*-value of the non-parametric Mann-Whitney test for a difference between control and treatment groups.
[b] Adjusted mean difference of the V4 outcome by ANCOVA analysis, adjusted on the baseline value (V1) and the clinical centre (Bordeaux or Toulouse). A negative value indicates that the value for the treatment group is lower than the value for the control group.
[c] *P*-value of the adjusted mean difference.

Table 3
Effect of the intervention on periodontal outcomes.

Periodontal outcomes	*n*	Control group Mean ± SD	*n*	Treatment group Mean ± SD	*P*[a]	Adjusted Mean Difference[b] aMD [CI95%]	*P*[c]
Periodontal pocket depth – PPD (mm)							
V1	11	2.27 ± 0.53	11	2.36 ± 0.59	0.70	−0.17 [−0.37; 0.03]	0.09
V4	10	2.22 ± 0.43	9	2.01 ± 0.56	0.22		
Clinical attachment loss – CAL (mm)							
V1	11	2.71 ± 1.37	11	3.03 ± 1.12	0.27	−0.17 [−0.53; 0.18]	0.31
V4	10	2.78 ± 1.29	9	2.66 ± 1.20	0.81		
Recession - REC (mm)							
V1	11	0.52 ± 1.09	11	0.66 ± 0.70	0.32	0.12 [−0.23; 0.47]	0.49
V4	10	0.51 ± 0.85	9	0.64 ± 0.89	0.18		
Bleeding on probing - BoP (%)							
V1	11	15.5 ± 12.1	11	12.0 ± 13.3	0.36	−11.8 [−24.7; 0.01]	0.07
V4	10	16.5 ± 19.0	9	4.0 ± 4.5	0.05		
Periodontal epithelial surface area – PESA (mm^2)							
V1	11	844.0 ± 188.2	11	837.2 ± 244.8	0.94	−127.7 [-246.5; −8.9]	0.04
V4	10	828.5 ± 221.1	9	677.4 ± 278.0	0.25		
Periodontal inflamed surface area – PISA (mm^2)							
V1	11	138.9 ± 130.3	11	122.53 ± 160.0	0.55	−91.8 [−172.2; −11.3]	0.03
V4	10	122.3 ± 107.9	9	30.6 ± 33.4	0.05		

Results are presented as mean ± standard deviation for the first visit (V1) and the visit in three months (V4).
[a] *P*-value of the non-parametric Mann-Whitney test for a difference between control and treatment groups.
[b] Adjusted mean difference of the V4 outcome by ANCOVA analysis, adjusted on the baseline value (V1) and the clinical centre (Bordeaux or Toulouse). A negative value indicates that the value for the treatment group is lower than the value for the control group.
[c] *P*-value of the adjusted mean difference.

Table 4
Effect of the intervention on quality of life outcomes.

Quality of life outcomes	*n*	Control group Mean ± SD	*n*	Treatment group Mean ± SD	*P*[a]	Adjusted Mean Difference[b] aMD [CI95%]	*P*[c]
General Oral Health Assessment Index – GOHAI							
Add-GOHAI (%)							
V1	11	0.74 ± 0.14	11	0.63 ± 0.24	0.37	0.10 [-0.12; 0.31]	0.37
V4	11	0.69 ± 0.24	11	0.71 ± 0.27	0.74		
Physical functioning (%)							
V1	11	0.77 ± 0.24	11	0.70 ± 0.26	0.46	-0.01 [-0.22; 0.21]	0.96
V4	11	0.76 ± 0.26	11	0.71 ± 0.28	0.67		
Pain and discomfort (%)							
V1	11	0.72 ± 0.25	11	0.60 ± 0.19	0.25	0.13 [-0.15; 0.40]	0.34
V4	11	0.67 ± 0.23	11	0.71 ± 0.28	0.51		
Psychosocial impacts (%)							
V1	11	0.74 ± 0.19	11	0.60 ± 0.30	0.20	0.13 [-0.07; 0.33]	0.20
V4	11	0.65 ± 0.28	11	0.70 ± 0.31	0.64		
Health Assessment Questionnaire - HAQ							
Disability Index							
V1	11	0.91 ± 0.59	10	1.31 ± 0.71	0.17	0.06 [−0.54; 0.65]	0.85
V4	10	0.75 ± 0.50	10	1.05 ± 0.70	0.32		
Dressing							
V1	11	0.91 ± 0.94	10	1.10 ± 0.74	0.60	-0.23 [−1.03; 0.56]	0.54
V4	10	0.70 ± 0.95	10	0.60 ± 0.70	0.97		
Rising							
V1	11	0.64 ± 0.67	9	1.00 ± 0.87	0.33	0.41 [−0.16; 0.99]	0.15
V4	10	0.20 ± 0.42	10	0.70 ± 0.82	0.13		
Eating							
V1	11	0.73 ± 0.79	10	1.30 ± 1.06	0.21	0.21 [−0.68; 1.10]	0.62
V4	10	0.80 ± 0.63	10	1.10 ± 0.99	0.54		
Walking							
V1	11	0.91 ± 0.83	10	1.00 ± 0.94	0.82	0.00 [−0.67; 0.67]	1.00
V4	9	0.56 ± 0.73	10	0.70 ± 0.82	0.72		
Hygiene							
V1	11	0.91 ± 1.14	10	1.80 ± 1.23	0.09	0.20 [−0.78; 1.18]	0.67
V4	10	0.70 ± 1.06	10	1.50 ± 1.18	0.09		
Reach							
V1	11	1.55 ± 0.93	10	1.50 ± 0.85	0.79	0.01 [−0.63; 0.65]	0.97
V4	10	1.70 ± 0.95	10	1.60 ± 0.84	0.81		
Grip							
V1	11	0.73 ± 0.90	10	1.20 ± 1.03	0.28	−0.08 [−0.91; 0.75]	0.84
V4	10	0.60 ± 0.97	10	0.80 ± 0.79	0.45		
Activity							
V1	11	0.91 ± 0.70	10	1.50 ± 0.53	0.05	0.20 [−0.79; 1.20]	0.67
V4	10	0.70 ± 0.82	10	1.40 ± 0.97	0.10		

Results are presented as mean ± standard deviation for the first visit (V1) and the visit in three months (V4).

[a] *P*-value of the non-parametric Mann-Whitney test for a difference between control and treatment groups.

[b] Adjusted mean difference of the V4 outcome by ANCOVA analysis, adjusted on the baseline value (V1) and the clinical centre (Bordeaux or Toulouse). A negative value indicates that the value for the treatment group is lower than the value for the control group.

[c] *P*-value of the adjusted mean difference.

that 15 of the 17 patients were being treated with Abatacept. Abatacept is a selective T-cell co-stimulation inhibitor [27]. No study has been published on the consequences of this specific biologic agent on observed periodontal clinical conditions. We could make an analogy with lower baseline BoP values observed with an anti-IL6 monoclonal antibody compared to tumour necrosis factor inhibitors [28]. Better periodontal health might also be linked to the encouragement to practice oral hygiene before biotherapies are introduced. If gingival inflammatory status is in fact lower than in other studies, the margin for periodontal inflammation improvement may have been insufficient to obtain a clinical improvement in RA [29].

Unlike other studies with moderately active RA [8,9,30,31], we did not demonstrate a decrease in DAS28, swollen joints, CRP or ESR despite a clinical reduction in periodontal inflammation. Another reason could be the type of RA patients included, since approximately 90% of the participants had long-term and severe RA, with HAQ ≥ 0.5 (Table 1). In other studies, RA duration was usually shorter [30–32] and baseline HAQ values were hardly ever reported [32]. The complexity of the intrinsic pathophysiological mechanisms of RA [5], the chronic ailments with significant sequelae, and the many confounding factors between periodontitis and polyarthritis, may explain the lack of effect of periodontal treatment in such a study; the focal infection theory as a causal relationship still being in debate [33].

Third, to our knowledge, this trial is the first to investigate the effect of periodontal treatment on quality of life in RA patients. The GOHAI was used to evaluate the OHRQoL [18]; it highlights the subject's daily experience, and can determine functional problems, discomfort and pain [12]. In some previous studies the oral quality of life in RA patients was worse [13,14]. It is known that periodontitis affects OHRQoL [34] and that non-surgical periodontal treatment can improve OHRQoL [35], particularly in terms of function, psychology and pain [36]. In this study, there was a tendency

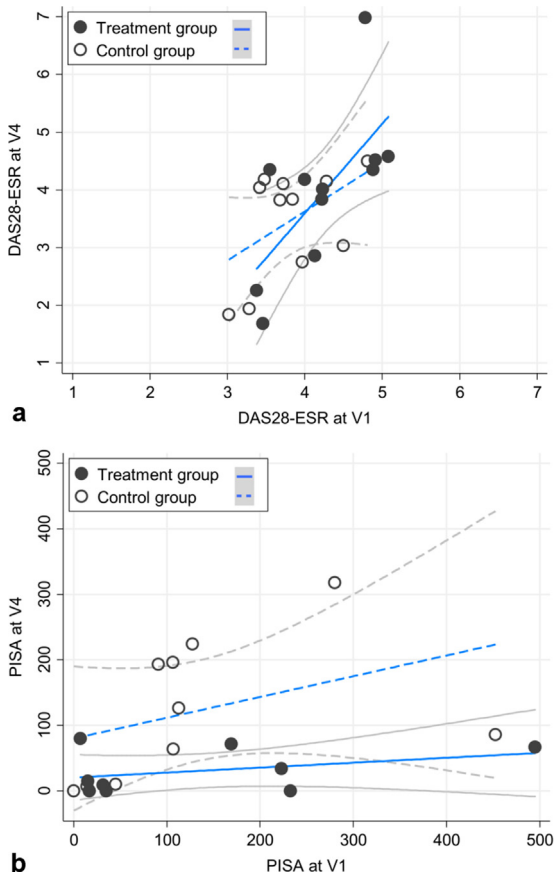

Fig. 2. a: scatter plot of the relationship between DAS28-ESR at V1 and V4 for the control (clear circles) and treatment groups (black circles). The linear regression line is shown in blue (solid for the treatment group and dashed for the control group) along with 95% confidence intervals; b: scatter plot of the relationship between PISA at V1 and V4 for the control (clear circles) and treatment groups (black circles). The linear regression line is shown in blue (solid for the treatment group and dashed for the control group) along with 95% confidence intervals.

towards psychological improvement. In terms of the patients' overall quality of life, the HAQ disability index was used. We found no significant changes in the HAQ index, as previously suggested [32], or in any of the eight HAQ subdomains.

Several limitations should be considered. First, it is likely that ESPERA participants are not representative of RA patients, even within France. This study mainly enrolled patients admitted to the outpatient Rheumatology units of the Regional University Hospitals of Toulouse and Bordeaux. These are referral units for RA diagnosis and management in the southwest of France. These patients have long-term, severe, ACPA positive, even refractory RA that is essentially treated with biological DMARDs (Table 1). It might be interesting to repeat a similar intervention on other categories of RA patients, such as early RA patients [37]. Second, the main limitation of this work is the small sample size available for analysis, which did not reach the levels calculated a priori. We had to stop inclusions because no effect trend was found in an interim analysis, in a context where the inclusion of participants was difficult. According to the treat-to-target approach, tight control principles of RA management, frequent adjustments of therapeutics (in dosage or type of molecule) were therefore necessary if there was no improvement in three months at most after the start of treatment, or if the target had not been reached by six months (remission or low disease activity) [38]. Consequently, it was very difficult to enrol patients with a DAS28 score between 3.2 and 5.1 and who had also had no change in medication, dose, or RA treatment formulation in the three months preceding inclusion [14]. Under these circumstances, it would not have been ethical to pursue inclusions, and amending the protocol to adapt to these new practices would have profoundly disrupted the analyses. The absence of significant improvement on the DAS28 after periodontal treatment could therefore be interpreted as insufficient power to demonstrate an effect. Nevertheless, even if we initially planned to enrol 16 participants per group to be able to detect a difference of 0.6 point in DAS28-ESR between the two groups, it would be unlikely that achieving this objective would have revealed a statistically significant difference according to the absence of any quantitative difference in the 3-month change of DAS28-ESR between the two groups of 11 participants (−0.03 [−0.98;0.92], $P = 0.95$). Lastly, although the plaque control record is important to assess participant compliance with oral hygiene instructions, we did not consider this data to be essential because the focus was on the ITT analysis.

Although this trial found no clinical effect of periodontal treatment on RA, it provides important data to support periodontal care among RA patients. Periodontal treatment is safe and reduces oral inflammation with a possible effect on oral health QoL. Since both periodontitis and RA are complex and multifactorial chronic diseases, it is likely that person-centred approaches that involve both oral health professionals and rheumatologists will contribute to optimal patient management [39,40].

Disclosure of interest

P.M., A.C. and JN.V. declare they are currently involved in a Cochrane systematic review entitled "Interventions for periodontal disease in people with rheumatoid arthritis". The other authors declare they have no conflicts of interest in connection with this article.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2019.02.006.

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