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Treatment of severe periodontitis may improve clinical disease activity in otherwise treatment-refractory rheumatoid arthritis patients

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Key message: RA patients with treatable periodontitis are highly prevalent among those with multiple resistance to DMARD's.

Sir,

immune responses against a large variety of citrullinated peptides are a hallmark of RA, with the periodontal tissue proposed as a key source of antigens. Dysbiosis in the oral microbiome during periodontitis is also associated with the onset of RA and auto-antibody generation, however links between different microbial communities and distinct autoantibody fine specificities require further clarification (1,2).

Treatment of periodontitis may induce remission in early RA (3), but did not affect disease activity in established RA in the ESPERA trial (4). In this registered study (NCT02096120; ethical approval: KEK-BE 130/13) we investigated the hypothesis that persistent infectious triggers of RA disease activity accumulate in the periodontium of people who cannot be successfully treated with multiple anti-rheumatic therapies. We recruited patients with inadequate response to at least two conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) and at least two immune target specific biological DMARDs (bDMARDs). All patients had erosive RA, and high levels of both anti-cyclic citrullinated peptide antibodies (CCP) and rheumatoid factor. Eight out of ten screened patients (mean DAS₂₈ 5.1 [IQR 4.8, 5.8]) exhibited loss of periodontal clinical attachment level (CAL) ≥ 5 mm at least in two separate sites, fulfilling treatment criteria. Treatment comprised one-stage full mouth disinfection, in conjunction with intensified oral hygiene instruction, plus one week of amoxicillin (500 mg, three times a day for seven days prescribed in seven cases), or alternatively azithromycin (500 mg once daily for three days given in one patient with a history of intolerance to beta-lactam antibiotics), plus metronidazole therapy (500 mg three times

daily for seven days in all eight treated patients) (5). At baseline, and three and six months after treatment, periodontal inflammation was monitored by assessing CAL, probing depth and bleeding on probing rates (BOP), along with RA disease activity measured by the disease activity disease index (6) based on 28 joints, microbial colonization in the gingival crevicular fluid, and serum antibody repertoire against specific citrullinated peptides.

Successful periodontal treatment was demonstrated by improved mean CAL ($p=0.018$), and reduced mean probing depth ($p=0.051$) and mean BOP ($p=0.018$) at three months in all treated patients. Five out of eight patients exhibited an improvement in DAS28_{ESR} of at least 0.6 points (DAS₂₈ responders) at 3 months. We considered these individuals to be clinical responders (6). Periodontitis was more severe at baseline, but improved more profoundly upon intervention, in DAS₂₈ responders (**Tab. 1**). Eleven periodontopathogenic bacterial species were monitored in the subgingival biofilm, using a semiquantitative nucleic-acid based detection method (Micro-IDent®plus11, Hain Lifescience Nehren, Germany). *Aggregatibacter actinomycetemcomitans* was not detected in any sample at levels above 10^6 bacteria. In two patients *Porphyromonas gingivalis* was present at baseline at levels higher than 10^6 , and in both subjects levels were reduced 3 months after treatment. However, *Porphyromonas gingivalis* colonisation at month 6 returned to baseline levels. Of these two patients, one had a clinical response with a change in DAS28_{ESR} from 4.4 at baseline to 3.2 at month 3. The other of these two patients was a non-DAS₂₈-responder. *Prevotella intermedia* was present in high amounts at baseline in one patient. Following treatment, *Prevotella intermedia* DNA levels were reduced only in this patient with maintained DAS₂₈ response over 6 months, characterised by a course in DAS28_{ESR} of 5.0 at baseline to 2.7 at month 3 and 2.3 at month 6, with undetectable bacterial load observed at month 3 and maintained at month 6. *Capnocytophaga*, a group of periodontopathogenic species linked with rheumatoid factor positivity in the Third National

Health and Nutrition Examination Survey (NHANES-III) cohort without RA (7), was observed significantly more frequently at baseline in patients who went on to show a DAS₂₈ response >0.6 points, compared to non-responders. Colonization by *Capnocytophaga species* was reduced three months after intervention in three out of the four moderate DAS₂₈ responders; the fourth patient declined dental follow-up examinations. Serum concentrations of anti-citrullinated tenascin-C (cTNC5) antibodies were significantly higher at baseline in patients without a DAS₂₈ response than in DAS₂₈ responders (**Tab. 1**). However, none of the tested autoantibody titres significantly changed upon periodontal therapy.

In summary, we identified a substantial proportion of cases with a high degree of periodontitis in this cohort of people with RA who do not respond well to several rounds of treatment with different DMARDs. Besides the known association between periodontitis and RA, this study might also imply negative effects of an intensive programme of immune-modulating RA therapy on oral health. DAS₂₈ response in five out of these eight patients following treatment for their periodontitis appears promising, though clinical responses did not track back to specific periodontopathogens or changes in antibody titres against specific citrullinated epitopes. These data reveal that consideration of the clinical severity of periodontitis, and associated microbial communities, may be important co-factors for the design of future interventional trials.

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Table 1

Baseline characteristics (non italic) and change in secondary periodontitis outcome parameters from baseline to month 3 (in italics), stratified by DAS28_{ESR} improvement of at least 0.6 points upon periodontitis therapy at month 3. Statistics for binary variables were Fisher's exact test and for quantitative data Wilcoxon's rank sum test.

Parameter	Unit	Non-responder (n=3)	Responder (n=5)
Age	[years]	62±13	61±10
Female	n=	3	3
Body mass index	[kg/m ²]	27±7	29±5
Disease duration	[years]	18±10	10±6
Previous csDMARDs	n, median	2	2
Previous bDMARDs	n, median	6	5.5
DAS28 _{ESR} *	Mean ± SD	5.7±0.4	4.8±0.3
Total number of teeth	Median [IQR]	20 [8; 21]	14 [8; 16]
Number of pockets > 4mm	Median [IQR]	15 [7; 17]	14 [8; 15]
Probing depth	mm, median [IQR]	3.1 [2.6; 3.4]	3.9 [3.8; 3.9]
<i>Change in probing depth</i>	<i>mm, median [IQR]</i>	<i>1.0 (0.9-1.1)*</i>	<i>1.4 [1.2-1.5], n=4</i>
Clinical Attachment level (CAL)**	mm, median [IQR]	-3.5 [-5; -2.2]	-6.9 [-7; -6.6]
<i>Change in CAL</i>	<i>mm, median [IQR]</i>	<i>0.2 [0-1.1]*</i>	<i>1.2 [0.9-1.4], n=4</i>
Bleeding on probing (BOP)	Sites in %, median [IQR]	27 [18; 83]	40 [35; 46]
<i>Change in BOP</i>	<i>Sites in %, median [IQR]</i>	<i>-19 [-48, -7]</i>	<i>-32 [-40, -20], n=4</i>
O'Leary plaque index	Median [IQR]	34 [16; 52]	80 [0; 91]
A. actinomycetemcomitans	N	0	0
Porphyromonas gingivalis	N	1	1

Prevotella intermedia	N	0	1
Capnocytophaga sp. [#]	N	1	4
Rheumatoid factor	IU/ml	420 [63; 777]	157 [137; 561]
CCP antibodies	IU/ml	169 [155; 183]	190 [188; 191]
rVim	OD, median [IQR]	0 [0; 0.008]	0 [0; 0]
cVim	OD, median [IQR]	0.026 [0.01; 1.344]	0.078 [0.043; 0.098]
rFib	OD, median [IQR]	0 [0; 0.038]	0 [0; 0]
cFib	OD, median [IQR]	0.286 [0.001; 0.694]	0.158 [0.109; 0.674]
REP-1	OD, median [IQR]	0.008 [0.003; 0.012]	0.004 [0.001; 0.006]
CEP-1	OD, median [IQR]	0.026 [0.01; 0.349]	0.013 [0.013; 0.452]
rTNC5	OD, median [IQR]	0.061 [0.037; 0.063]	0.038 [0.029; 0.041]
cTNC5**	OD, median [IQR]	0.085 [0.074; 0.215]	0.051 [0.037; 0.054]

*p=0.03, **p=0.05, #p=0.014. Abbreviations: IQR: interquartile range, IU: international unit, SD:

standard deviation. rVim: antibodies against arginine baring, cVim, antibodies against citrullinated

vimentin peptides. rFib and cFib = antibodies against fibrinogen, REP-1 and CEP-1 = antibodies

against enolase and rTNC5 and cTNC5 against tenascin-C.