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Effect of anti-rheumatic agents on periodontal parameters and biomarkers of inflammation: a systematic review and meta-analysis

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Purpose: Anti-rheumatic agents target common molecular pathways of inflammation in rheumatoid arthritis (RA) and periodontitis. The purpose of this study was to determine the relative effect of anti-rheumatic agents on the levels of inflammatory biomarkers and periodontal inflammation in RA patients with periodontitis.
Methods: A systematic review and meta-analysis were conducted of studies comparing periodontal parameters of inflammation, such as bleeding on probing, and biomarkers of inflammation in RA patients with periodontitis and healthy adults with and without periodontitis. The search included the electronic databases MEDLINE, Cochrane Database of Systematic Reviews, and Google Scholar, inclusive through October 2011, with no language restrictions. Hand searches were conducted of the bibliographies of related journals and systematic reviews. Observational and interventional studies assessing the effects of anti-rheumatic therapy qualified for inclusion. Two reviewers performed independent data extraction and risk-of-bias assessment. Of the 187 identified publications, 13 studies fulfilled the inclusion criteria.
Results: When compared to healthy adults without periodontitis, RA subjects were found to have significantly higher levels of bleeding on probing and limited evidence of higher levels of interleukin-1β and tumor necrosis factor-α (TNF-α) in gingival crevicular fluid and saliva. No consistent differences were found in periodontal parameters and inflammatory biomarkers between RA subjects and adults with periodontitis. Studies evaluating the effect of anti-TNF-α therapy in RA subjects with periodontitis have yielded inconsistent results.
Conclusions: There are limited data, however, to suggest that anti-TNF-α agents can reduce local production of inflammatory cytokines and periodontal inflammation in RA patients with periodontitis.

Keywords: Periodontitis, Rheumatoid arthritis, Tumor necrosis factor-alpha.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease affecting 0.5 to 1.0% of the population, with women carrying a disproportionately higher risk (3:1) of disease than men [1]. RA is a polyarthritis characterized by chronic inflammation, synovial hyperplasia, and intra-articular fibrin deposition leading to destruction and deformity of the joint architecture and function. Similar to chronic periodontitis, the clinical onset of RA frequently occurs after the ages of 35 years. Although the etiology of RA remains incompletely understood, the initiation and propagation of the disorder have been at-

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tributed to multiple factors, including low-grade infection and auto-antigens. Sustained elevations in pro-inflammatory mediators following disease initiation, such as subclinical infection, appear necessary for progression [2].

Overlapping molecular pathways of inflammation have been implicated in periodontitis and rheumatoid arthritis. Periodontitis has been associated with elevations in circulating levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) [2]. Moreover, *Porphyromonas gingivalis* has been associated with an enhanced inflammatory response expressed by higher CRP levels [3]. Periodontitis and RA are characterized by similar humoral and cellular immune responses and a common immunogenetic profile [4]. Microscopically, the inflammatory lesions and tissue destruction observed in RA share similarities with those found in periodontitis [5]. Local tissue destruction involves the production of inflammatory cytokines and proteolytic proteins, such as matrix metalloproteinases (MMPs) [6]. The prevalence of RA in patients with periodontitis has been found to be nearly four times the rate of the general population (3.95% vs. 1%, respectively) [7]. The association of periodontitis with RA appears to be independent of other risk factors, including cigarette smoking, socioeconomic status, body mass index, alcohol consumption, and poor oral hygiene [8].

Several hypotheses have been advanced to explain the association between RA and periodontitis. Evidence of *Porphyromonas gingivalis*, *Tannerella forsythensis* and *Prevotella intermedia* has been identified in the synovial fluid in RA, suggesting that periodontal pathogens play a role in disease initiation or propagation [9]. Viral infections have been implicated as an environmental risk factor for rheumatoid arthritis [10] and periodontitis [11]. Antibodies against cyclic citrullinated peptide have been identified in many RA patients [12]. Citrullination is the post-translational conversion of arginine residues to citrulline residues by the enzyme peptidylarginine deiminase (PAD) [13]. *P. gingivalis* has been shown to express the PAD protein and may play a crucial role in the pathogenesis of periodontitis-associated RA [5]. Collectively, these observations suggest that common molecular pathways underlie each of these inflammatory conditions [2].

The presence of shared underlying inflammatory pathways mediating the progression of periodontitis and RA should provide potentially important common therapeutic targets. The purpose of this study, therefore, was to determine the relative effect of anti-rheumatic agents (Table 1) on levels of periodontal inflammation and inflammatory biomarkers in RA patients with periodontitis. A systematic review and meta-analysis were conducted of studies comparing periodontal parameters of inflammation and biomarkers of inflammation in RA patients with periodontitis and healthy adults with and without periodontitis.

Table 1. Drugs used in the treatment of rheumatoid arthritis.

Type of drugs	Therapeutic agent	Target	Disadvantages
NSAIDs	Aspirin	Inhibition of the synthesis of cyclooxygenase	No change in the progression of disease
	Naproxen		
	Diclofenac		
	Ibuprofen		
DMARDs	Methotrexate	Change the progression of disease	Toxicity
	Leflunomide		No change in the progression of erosive articular damage
	Sulphasalazine		
	Hydoxychloroquine		
Anti-cytokines	Infliximab	Tumor necrosis factor-α	Infection, malignancy
	Etanercept		
	Adalimumab		
	Golimumab		
	Certolizumab		
	Anakinra	Interleukin (IL)-1	Limited efficacy in reducing progression of disease, infection risk
	Tocilizumab	IL-6	Potential to affect host defense
	Abatacept	T-cell activation	Infection risk
	Rituximab	B-cell depletion	Infection risk

NSAIDs: non-steroidal anti-inflammatory drugs, DMARDs: disease modifying antirheumatic drugs.

MATERIALS AND METHODS

Study selection and interventions

The eligibility criteria for inclusion in thesystemic review were: 1) human subjects with RA undergoing anti-rheumatic therapy, 2) evaluation of periodontal indices or biomarkers of inflammation in serum, saliva, or gingival crevicular fluid, 3) case-control or randomized controlled study design, and 4) English language publications. Exclusion criteria included case reports and review articles (Fig. 1).

Data sources and search

The bibliographical databases MEDLINE, Cochrane Database of Systematic Reviews, and Google Scholar were searched up to and including October 2011 for studies examining the effects of anti-rheumatic therapy on periodontal status and biomarkers of inflammation in serum, saliva, or gingival cre-

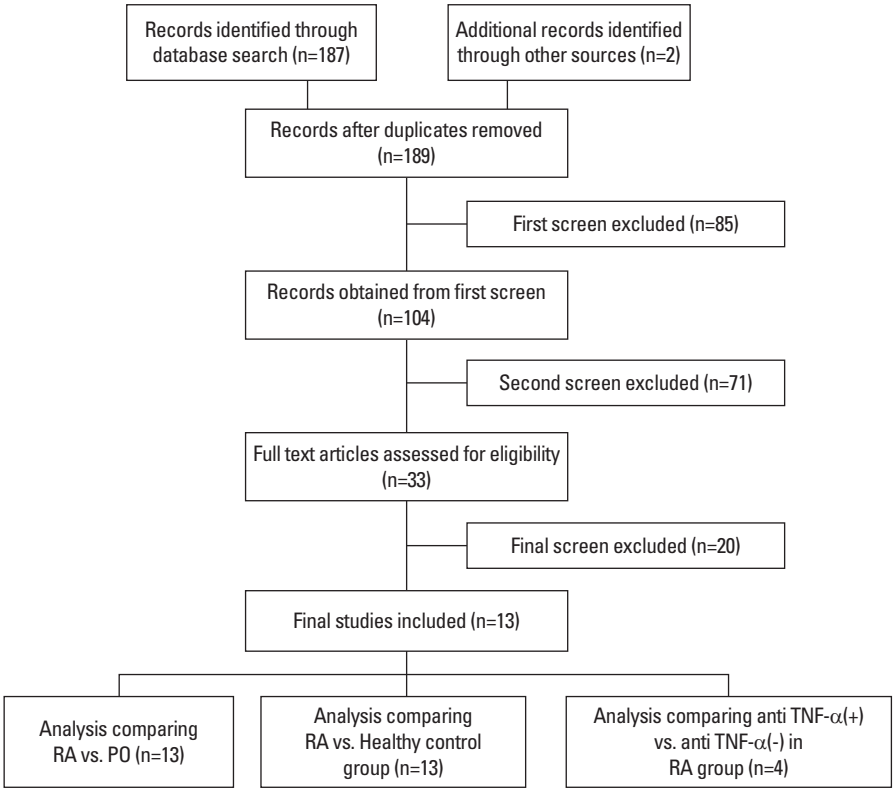

Figure 1. Flowchart of literature identification, screening, eligibility, and inclusion process. RA: rheumatoid arthritis, PO: periodontitis, TNF-α: tumor necrosis factor-α.

vicular fluid (GCF) in RA subjects. In addition to the online search, a hand search was conducted of the bibliographies of the articles identified and their related journals.

The authors assessed all data independently and disagreements were resolved by discussion. Online search terminology included "periodontitis and/or rheumatoid arthritis" and "drug(s) and/or anti-TNF-α or therapy." Abstracts were also identified that required full text access to assess inclusion or exclusion in this systematic review. For the second-stage screening, studies using the same population surveys or databases were identified to avoid duplicate inclusion. Full text copies were obtained of the remaining non-excluded articles. In the final screening, full-text papers were eligible for inclusion provided that data were available on the periodontal status and biomarkers of inflammation.

Data extraction and quality assessment

In addition to the basic features of research design, data were extracted on the biomarkers of inflammation (e.g., CRP, IL-1β, TNF-α) and clinical measures of periodontal status, including gingival inflammation and bleeding on probing. Measures of bacterial plaque accumulation were also recorded for comparison.

Studies evaluating the effect of anti-rheumatic agents in RA subjects permitted comparisons with 1) healthy subjects, 2) periodontitis subjects, and 3) RA subjects not on anti-rheumatic agents. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [14] was used as a general guideline for communicating the results of this investigation.

Statistical analysis

The mean final score for each outcome measure was submitted to a meta-analysis, including an assessment for heterogeneity (Comprehensive Meta-Analysis, Biostat Inc., Englewood, NJ, USA). Meta-analysis permitted comparisons of-subjects between groups (RA vs. healthy) as well as a comparison of RA subjects based on treatment with anti-TNF-α medication. A meta-analysis comparing the standard difference in means (SDM) was computed for each outcome measure, when data were available from 3 or more studies, using a random-effects model, with an α-level set at $P \leq 0.05$. Studies in the analysis were weighted according to the number of subjects contributing scores in each treatment group.

RESULTS

The initial online search identified 187 publications, with

Table 2. Characteristics of the studies included in meta-analysis.

Study	RA patients				Healthy controls			Periodontitis controls		
	Age (year)	Duration of RA (year)	Periodontal status	Smokers	Age (year)	Periodontal status	Smokers	Age (year)	Periodontal status	Smokers
Bozkurt et al. [21] (2000)	47.8±6.4	1-8	Generalized moderate periodontitis PD: 3.61±0.84 CAL: 4.59±1.29	Not specified	45.67±7.16	Clinical criteria not specified PD: 1.80±0.25 CAL: 1.84±0.38	Not specified	47.1±6.9	Generalized moderate periodontitis PD: 3.87±0.81 CAL: 4.89±1.39 Clinical parameters not specified	Not specified
Havemose-Poulsen et al. [23] (2005)	18-35	Not specified	1999 International Workshop[a] Clinical parameters not specified	Not specified	18-35	No interproximal attachment loss and no signs of other inflammatory conditions Clinical parameters not specified	Not specified	18-35	1999 International Workshop[a] LAgP GAgP	Not specified
Biyikoglu et al. [19] (2006)	52.6±9.9	15.8±8.3	1999 International Workshop[a] Clinical parameters not specified	21.7% (5/23)	Not specified	Clinical criteria not specified No CAL, PD<3 mm No sign of clinical inflammation Clinical parameters not specified	5.9% (1/17)	49.1±6.6	1999 International Workshop[a]	35.2% (6/17)
Bozkurt et al. [22] (2006)	47.1±11.3	Not specified	Chronic periodontitis Clinical and radiographic criteria (CAL >2 mm at 2 or 3 sites in more than 3 teeth in each quadrant, and radiographic evidence of bone loss) Clinical parameters not specified	Non smokers	36.2±3.5	Clinical and radiographic criteria (No CAL> 2 mm at 2 or 3 sites in more than 3 teeth in each quadrant, and radiographic evidence of bone loss) Clinical parameters not specified	Non smokers	43.8±9.6	Chronic periodontitis Clinical and radiographic criteria (CAL > 2 mm at two or three sites in more than 3 teeth in each quadrant, and radiographic evidence of bone loss) Clinical parameters not specified	Non smokers
Havemose-Poulsen et al. [24] (2006)	30.0±4.0	5±4.2	1999 International Workshop[a] PD≥4 mm, CAL≥2 mm ABL≥2 mm	30.4% (7/23)	25.0±3.1	No interproximal attachment loss and no signs of other inflammatory conditions Clinical parameters not specified	4% (2/25)	LAgP:20.0±5.2 GAgP:32.0±3.3	1999 International Workshop[a] PD≥4 mm, CAL≥2 mm ABL≥2 mm Clinical parameters not specified	LAgP:16.7% (3/18) GAgP:74.1% (20/27)
Miranda et al. [17] 2007	49.5±10.6	12.1±9.9	PI, Marginal bleeding, BOP, PD, CAL Clinical parameters not specified	41.2% (7/17)[b]	48.6±11.2	PI, marginal bleeding, BOP, PD, CAL Clinical parameters not specified	41.2% (7/17)[b]			
Nilsson et al. [18] (2008)	49.0±10.0	14±8.4	BOP, PD, CAL Clinical parameters not specified	Non smokers	29-61	BOP, PD, CAL Clinical parameters not specified	Non smokers			
Biyikoglu et al. [20] (2009)	52.6±9.9	16.4±9.8[c]	1999 International Workshop[a] Clinical parameters not specified	16% (4/25)	49.1±6.6	No CAL, PD<3 mm No sign of clinical inflammation Clinical parameters not specified	33.3% (8/24)	50.0±7.6	1999 International Workshop[a] Clinical parameters not specified	56% (14/25)
Mayer et al. [16] (2009)	RA(+):53.6±9.2 RA(-):47.1±16.1	RA(+):16.4±12.12 RA(-):4.6±2.12	1999 International Workshop[a] Clinical parameters not specified	RA(+):30% (3/10) RA(−):30% (3/10)	51.5±9.9	1999 International Workshop[a] Clinical parameters not specified	50% (5/10)			
Kobayashi et al. [15] (2010)	59.7±1.4	LDA: 15.3±2 MDA+HAD: 15.7±1.4	BOP, PD, CAL Clinical parameters not specified	7.1% (6/84)	57.6±1.8	BOP, PD, CAL Clinical parameters not specified	9.1% (2/22)			
Mirrielees et al.[25] (2010)	46.8±10.5	At least 3 years after diagnosis	1999 International Workshop[a] BOPsites : 13.0±10.4 PD sites≥4 mm: 4.9±8.6 PD sites≥5 mm: 1.7±3.4 CAL≥2 mm: 3.4±6.7	11.4% (4/35)	43.0±10.6	1999 International Workshop[a] BOPsites: 4.6±5.5 PD sites≥4 mm: 1.8±2.3 PD sites≥5 mm: 0.2±0.5 CAL≥2 mm: 2.7±5.9	0% (0/35)	44.2±8.2	1999 International Workshop[a] BOPsites: 55.0±23.5 PD sites≥4 mm: 27.0±15.0 PD sites≥5 mm: 16.4±11.4 CAL≥2 mm: 17.6±11.8	17.1% (6 /35)

RA: rheumatoid arthritis, PD: probing depth, CAL: clinical attachment level, LAgP: localized aggressive periodontitis, GAgP: generalized aggressive periodontitis, ABL: alveolar bone level, BOP: bleeding on probing, LDA: disease activity score-28 (DAS28)-C-reactive protein (CRP)<3.2, MDA: 3.2≤ DAS28-CRP<5.1, HAD: DAS28-CRP≥5.1.

[a]1999 International Workshop for a Classification of Periodontal Diseases and Conditions (Armitage GC. Ann Periodontol 1999;4:1-6.), [b]Including 4 former smokers, [c]RA subjects with periodontitis.

only 13 studies fulfilling the inclusion criteria (Table 2). Four studies comparing RA subjects to healthy adults without periodontitis were excluded from analysis because the studies did not include selection criteria defining periodontal status [15-18]; however, one of these studies [16] also provided comparative data for RA subjects and healthy subjects with periodontitis and therefore, the study was included in this analysis. The RA subjects were treated with one or more anti-rheumatic therapies, including corticosteroids, non-steroidal anti-inflammatory drugs, disease modifying antirheumatic drugs (DMARDs), biologics, or anti-TNF-α agents [15-27]. Studies included RA subjects with periodontitis [15,18-24,26]. The RA subjects without periodontitis in one study were excluded from the analysis [27]. Methodological quality or risk of bias in the studies was considered moderate.

Comparison of RA subjects with periodontitis and healthy subjects without periodontitis

RA subjects were found to have significantly higher plaque index (PI) scores than healthy subjects without periodontitis (SDM=1.6; Z=3.1; $P \leq 0.05$); however, heterogeneity in PI scores between studies was significant (Q-value=49.8; $P \leq 0.001$) [15-17,19-22,24,26,27]. Higher mean gingival index (GI) scores in RA subjects than healthy subjects were reported in 2 studies [21,22]. Five studies provided comparative data demonstrating higher levels of bleeding on probing (BOP) [19-21,24,25] in RA subjects with periodontitis than healthy subjects without periodontitis (SDM=1.6; Z=4.2; $P \leq 0.001$) (Table 3). The heterogeneity in GI scores between studies was significant (Q-value=19.8; $P \leq 0.001$).

Some limited comparative data are available on the levels of inflammatory markers (IL-1β, IL-6, and IL-10) in RA subjects receiving anti-rheumatic therapy and healthy subjects without periodontitis [15,18,19,21,23,25] (Table 3). IL-1β levels were found to be higher in RA subjects in 2 of 3 studies [17,19,25]; however, the overall mean difference in IL-1β levels between subjects did not differ significantly (SDM=0.48; Z=1.76; $P \leq 0.08$). The variability in differences in IL-1β levels between studies was not significant (Q-value=4.7; $P \geq 0.05$). Higher levels of TNF-α were found in the saliva [25] but not the serum [23] of RA subjects compared to healthy subjects. RA subjects were also reported to have higher circulating CRP [24] and crevicular fluid MMP-8 [20] levels than healthy subjects.

Table 3. Comparison of inflammatory biomarkers and periodontal parameters in RA subjects and healthy subjects without periodontitis.

Study	Study design	Healthy (No.)	RA (No.)	Anti-rheumatic therapy	Periodontal status of RA subjects	Source	Biomarker						Periodontal measure		
							IL-1β	TNF-α	IL-6	IL-10	MMP-8	CRP	PI	GI	BOP
Bozkurt et al. [21] (2000)	Case-control	15	15	Corticosteroid NSAIDs DMARDs	Periodontitis	GCF			NS				↑	↑	↑[a]
Havemose-Poulsen et al. [23] (2005)	Cross-sectional	25	22	Corticosteroid NSAIDs DMARDs	Periodontitis	Serum	NS	NS	NS	↑					
Biyikoglu et al. [19] (2006)	Case-control	17	10	Corticosteroid NSAIDs	Periodontitis	GCF	↑						↑		↑
Bozkurt et al. [22] (2006)	Case-control	17	17	Corticosteroid NSAIDs DMARDs	Periodontitis	GCF				↓			↑	↑	
Havemose-Poulsen et al. [24] (2006)	Case-control	25	22	Corticosteroid NSAIDs DMARDs OP N-OP	Periodontitis	Serum						↑	NS		NS
Biyikoglu et al. [20] (2009)	Case-control	24	13	Corticosteroid NSAIDs	Periodontitis	GCF					↑		↑		↑
Mirrielees et al. [25] (2010)	Case-control	35	35	DMARDs Anti-TNF medication	Periodontitis[b]	Saliva	↑	↑					NS		↑

RA: rheumatoid arthritis, IL-1β: interleukin-1β, TNF-α: tumor necrosis factor-α, MMP-8: matrix metalloproteinase-8, CRP: C-reactive protein, PI: plaque index, GI: gingival index, BOP: bleeding on probing, NSAIDs: non-steroidal anti-inflammatory drugs, DMARDs: disease modifying anti-rheumatic drugs, GCF: gingival crevicular fluid, OP: opioid analgesics, N-OP: non-opioid analgesics, NS: $P>0.05$, ↑: significantly higher in RA subjects ($P<0.05$), ↓: significantly lower in RA subjects ($P<0.05$).
[a]Sulcus bleeding index, [b]Included subjects without periodontitis.

Comparison of RA subjects with periodontitis and healthy subjects with periodontitis

Table 4 presents a comparison of RA subjects with periodontitis to otherwise healthy subjects with periodontitis. Similar levels of plaque deposits (SDM=0.7; Z=0.5; $P \geq 0.05$) and gingival inflammation, as reflected in BOP scores (SDM=0.52; Z=0.80; $P \geq 0.05$), were found in RA and healthy subjects with periodontitis. Significant heterogeneity in PI scores (Q-value=41.4; $P \geq 0.05$) and BOP scores (Q-value=76.4; $P \geq 0.05$) was found between studies.

With the exception of IL-β, evaluations of each biomarker have been limited to a single study [19-22,25]. Significantly lower levels of IL-β [25], lower levels of TNF-α [25], and higher levels of IL-4 [22] have been reported in RA and healthy subjects with periodontitis.

Effects of anti-TNF-α agents in RA subjects with periodontitis

Limited evidence is available on the effectiveness of anti-TNF-α agents in reducing periodontal inflammation and inflammatory biomarkers in RA subjects with periodontitis (Tables 5 and 6). Two studies reported lower mean GI scores in RA subjects receiving anti-rheumatic agents plus anti-TNF-α drugs compared to RA subjects receiving only anti-rheumatic agents. Three studies reported BOP scores in RA subjects receiving anti-TNF-α drugs; however, there was no overall effect of anti-TNF-α agents on BOP scores (SDM=-1.64; Z=-1.56; $P \geq 0.05$), reflecting, in part, the significant heterogeneity among studies (Q-value=25.7; $P \leq 0.001$) [16,25,26]. Two case-control studies have reported lower TNF-α levels in GCF and serum of RA subjects receiving anti-TNF-α drugs compared to non-treated RA subjects [16,25]. Mirrielees et al. [25] also found significantly lower serum IL-1β levels in RA

Table 4. Comparison of inflammatory biomarkers and periodontal parameters in RA and healthy subjects with periodontitis.

Study	Study design	Anti-rheumatic therapy	Periodontitis (No.)	RA (No.)	Periodontal status of RA subjects	Source	Biomarker						Periodontal measure		
							IL-1β	TNF-α	IL-6	IL-4	IL-10	MMP-8	PI	GI	BOP
Bozkurt et al. [21] (2000)	Case-control	Corticosteroid NSAIDs Chloroquine	15	15	Periodontitis	GCF			NS				↑	NS	NS[a]
Biyikoglu et al. [19] (2006)	Case-control	Corticosteroid NSAIDs	17	10	Periodontitis	GCF	NS						NS		NS
Bozkurt et al. [22] (2006)	Case-control	Corticosteroid NSAIDs Chloroquine	17	17	Periodontitis	GCF				↓	NS		NS	NS	
Biyikoglu et al. [20] (2009)	Case-control	Corticosteroid NSAIDs	25	13	Periodontitis	GCF						NS	NS		NS
Mirrielees et al. [25] (2010)	Case-control	DMARDs Anti-TNF medication	35	35	Periodontitis[b]	Saliva	↓	↓					↓		↓

RA: rheumatoid arthritis, IL-1β: interleukin-1β, TNF-α: tumor necrosis factor-α, MMP-8: matrix metalloproteinase-8, PI: plaque index, GI: gingival index, BOP: bleeding on probing, NSAIDs: non-steroidal anti-inflammatory drugs, GCF: gingival crevicular fluid, DMARDs: disease modifying anti-rheumatic drugs, NS: $P>0.05$, ↑: significantly higher in RA subjects ($P<0.05$), ↓: significantly lower in RA subjects ($P<0.05$).
[a]Sulcus bleeding index, [b]Included subjects without periodontitis.

Table 5. Studies evaluating the effectiveness of anti-TNF-α agents in RA subjects.

Study	Duration of RA (years±SD)	Periodontal status	Anti-TNF-α therapy positive (RA [+])		Anti-TNF-α therapy negative (RA [-])	
			Age (year)	Smokers	Age (year)	Smokers
Pers et al. [27] (2008)	Not specified	Periodontitis[a]	53.2±8.2	5/20 (25%)	55.4±12	11/20 (55%)
Mayer et al. [16] (2009)	RA(+):16.4±12.12 RA(-):4.6±2.12	Periodontitis[a]	53.6±9.23	3/10 (30%)	47.1±16.1	3/10 (30%)
Ortiz et al. [26] (2009)	Not specified	Periodontitis	39-87 (median, 63)	Not specified	42-68 (median, 49)	Not specified
Mirrielees et al. [25] (2010)	At least 3 years after diagnosis	Periodontitis[a]	46.8±10.5	RA(+)+RA(-): 11.4%	46.8±10.5	RA(+)+RA(-): 11.4%

TNF-α: tumor necrosis factor-α, RA: rheumatoid arthritis, NS: $P>0.05$.
[a]Included some subjects without periodontitis.

Table 6. Association of anti-TNF-α medication with levels of inflammatory biomarkers and periodontal inflammation in RA subjects.

Author	Study design	Total	Periodontal status of RA subjects	No. of anti-TNF-α(+)	No. of anti-TNF-α(-)	Source	Biomarker		Periodontal measure		
							IL-1β	TNF-α	PI	GI	BOP
Pers et al. [27] (2008)[a]	Case-control	17	Periodontitis	8	9				NS	↑[b]	↑[c]
Mayer et al. [16] (2009)	Case-control	20	Periodontitis[a]	10	10	GCF		↓	NS	↓	↓
Ortiz et al. [26] (2009)	Case-control[d]	20	Periodontitis	10[e]	10				NS	NS	NS
Mirrielees et al. [25] (2010)	Case-control	35	Periodontitis[a]	18	17	Saliva	↓	↓			↓

RA: rheumatoid arthritis, IL-1β: interleukin-1β, TNF-α: tumor necrosis factor-α, PI: plaque index, GI: gingival index, BOP: bleeding on probing, NS: $P>0.05$, ↑: significantly higher in RA subjects ($P<0.05$), ↓: significantly lower in RA subjects ($P<0.05$).
[a]Included subjects without periodontitis, [b]Modified gingival index, [c]Papillary bleeding index, [d]Administration of anti-TNF-α was not randomized, [e]Pre- and post-treatment comparison.

subjects receiving anti-TNF-α drugs compared to non-treated RA subjects.

DISCUSSION

Multiple observational studies [2,28] and experimental studies in laboratory animals have established an association between RA and periodontitis [29,30]. RA and periodontitis share many similarities in pathophysiology and clinical progression [2]. Early studies suggested that non-steroidal inflammatory agents might hold promise in controlling the progression of these disorders; however, this class of drugs has shown minimal or no effect on RA [31] and periodontitis [32]. The development of new anti-rheumatic agents, including DMARDs and biologics, that target specific molecular factors in the inflammatory cascade, offers the potential to slow or arrest the progression of these disorders [33].

In this systematic review, we examined the relative effect of anti-rheumatic agents on the levels of inflammatory biomarkers and periodontal inflammation in RA patients with periodontitis. Of particular interest were studies comparing the periodontal and inflammatory profile of RA patients on different anti-rheumatic agents to otherwise healthy adults with and without periodontitis. Studies were case-controlled in design [16,19-27], using study populations of convenience, with only one study matching for age and gender [25]. The smoking status of subjects was generally adjusted for in the statistical analysis, although 3 studies did not specify the smoking status of subjects [21-23]. RA was diagnosed according to the criteria of the American College of Rheumatology [34] in all but 3 studies, which did not specify the criteria for diagnosis [21,22,26]. The duration of RA was highly variable, ranging from 1 year to over 25 years; however, the duration from the time of diagnosis or treatment was not provided in 2 studies [22,23].

Currently, non-steroidal anti-inflammatory drugs and steroids are used early in treatment to reduce inflammation and pain and to slow joint damage in RA patients. Disease modifying antirheumatic drugs, including methotrexate, leflunomide, hydroxychloroquine, sulphasalazine, and minocycline, and immunosuppressants are frequently necessary to slow the progression of erosive articular damage over time. The latter drugs, however, are associated with significant risk of liver damage, bone marrow suppression, and severe lung infections [35]. Biologic therapies targeting cytokines also have been successfully used in controlling RA [35]. The latter agents block or antagonize the actions of TNF-alpha, which is considered the "master regulator" of the inflammatory response in both RA [36] and periodontitis [37].

Most studies compared RA patients with periodontitis to healthy adults without evidence of destructive periodontal disease [19-25]. RA patients were found to have higher plaque scores and BOP scores compared to healthy patients without periodontitis. Of the available studies examining the biomarkers of inflammation, the majority compared GCF or salivary levels rather than serum levels [16,21-23,25]. Limited comparative data are available on the inflammatory biomarkers in RA patients compared to systemically healthy patients without periodontitis. Levels of IL-1β and TNF-α were found to be higher in the GCF and saliva [17,19,25], but not the serum [23], in RA patients with periodontitis compared to healthy subjects without periodontitis. Higher levels of TNF-α were found in the saliva [25] but not the serum [23] of RA subjects. These latter studies provide limited evidence suggesting that elevations in local but not systemic levels of these inflammatory cytokines are present in RA patients, despite anti-rheumatic treatment, compared to healthy persons without periodontitis. Consistent with elevations in local TNF-α expression, RA patients were also found to have higher BOP scores compared to healthy controls.

RA patients on anti-rheumatic agents were found to exhibit lower local IL-1β and TNF-α levels than otherwise healthy patients with periodontitis. Local IL-4 levels were also found to be lower in RA patients than in periodontitis patients. Lim-

ited data suggest that RA patients receiving anti-TNF-α medication may exhibit lower local IL-1β and TNF-α levels as well as less gingival inflammation, based on GI and BOP scores, than patients with periodontitis. However, interpretation of this evidence is necessarily limited due, in part, to both the observational design and small number of studies.

Smoking is a significant modifiable risk factor for periodontitis [38]. Recent research suggests that long-term smoking markedly increases the risk of RA in men and women [39]. One possible mechanism for the higher prevalence of periodontitis in RA patients may reflect the increased risk for oral colonization by *P. gingivalis*, a causative agent of periodontitis [40]. These observations are consistent with the hypothesis that *P. gingivalis*, which expresses PAD, plays a crucial role in the initiation and/or propagation of periodontitis-associated RA [5]. In studies included in this meta-analysis, the percentage of RA subjects that smoked ranged from about 7 to 41%; however, 2 studies excluded smokers and 2 studies did not specify the smoking status.

Ortiz et al. [26] reported that anti-TNF-α therapy without periodontal treatment had no significant effect on the periodontal condition. RA patients receiving periodontal treatment had a significant decrease in the mean RA disease activity score, the erythrocyte sedimentation rate, and serum TNF-α level. However, there was no clinical improvement in these parameters in patients that did not receive periodontal treatment. Anti-TNF-α therapy resulted in a significant improvement in gingival inflammation, BOP scores, and the clinical attachment level [26]. Pers et al. [27] evaluated the impact of an anti-TNF-α agent administered over a period of nearly 2 years on the periodontal status of 40 subjects with RA. Clinical attachment loss was significantly reduced after anti-TNF-α treatment, suggesting that TNF-α blockade in RA patients can limit periodontal breakdown. These results are consistent with the hypothesis that anti-TNF-α treatment is effective in improving periodontal status and reducing the biomarkers of inflammation.

RA and periodontitis share many similarities in pathophysiology and clinical progression, suggesting that treatment of RA with anti-rheumatic agents, particularly anti-TNF-α agents, may reduce the progression of destructive periodontal disease. Currently, insufficient evidence is available to determine whether traditional anti-rheumatic agents are beneficial in controlling periodontitis. There are limited data, however, suggesting that anti-TNF-α agents can reduce local production of inflammatory cytokines and periodontal inflammation in RA patients with periodontitis. Future studies are warranted to examine the benefits of TNF-α therapy in controlling periodontal inflammation and breakdown.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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