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INVITED REVIEW

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Impact of treatment of rheumatoid arthritis on periodontal disease: A review

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Abstract

Background: Numerous studies support a bidirectional association between rheumatoid arthritis (RA), a chronic autoimmune degenerative inflammatory joint disease, and periodontitis, a chronic inflammatory disease caused by the immune reaction to bacteria organized in biofilms. RA and periodontitis are both multifactorial chronic inflammatory diseases that share common modifiable and non-modifiable risk factors. There is no cure for RA; treatment is based on lifestyle modifications and a variety of medications: nonsteroidal anti-inflammatory drugs (NSAID), glucocorticoids, and disease-modifying antirheumatic drugs (DMARDs, e.g., conventional synthetic DMARDs [csDMARDs]; biological DMARDs [bDMARD] and targeted synthetic DMARDs). There are molecular pathways of inflammation that are common to both RA and periodontitis. Thus, there is a potential effect of RA treatments on periodontitis. This systematic review aims to assess the impact of antirheumatic agents on periodontal conditions of patients suffering from both RA and periodontitis.

Methods: PubMed/MEDLINE, Cochrane Library, and Embase online databases were systematically explored, and a manual search was performed to identify relevant studies published until January 2023. This review is registered in the PROSPERO database (CRD42023409006).

Results: A total of 2827 articles were identified, and 35 fulfilled the inclusion criteria. The included studies generally show a consensus that, at normal dosage, NSAID and corticosteroids have negligible impact on periodontium. Similarly, csDMARD alone or in combination with other csDMARD demonstrated no adverse effect on periodontium. Monotherapy with bDMARD had a positive effect on periodontal pocket depths and gingival inflammation in the longitudinal studies up to 6 months but showed

Abbreviations: ACPA, anti-citrullinated protein antibodies; BOP, bleeding on probing; bDMARDs, biological DMARDs; CAL, clinical attachment loss; csDMARDs, conventional synthetic DMARDs; DMARDs, disease-modifying antirheumatic drugs; GCF, gingival crevicular fluid; GI, gingival index; HCQ, Hydroxychloroquine; IL, interleukin; JAK, janus kinases; LM, leflunomide; MCP-1, monocyte chemoattractant protein-1; MTX, methotrexate; MMPs, matrix metalloproteinases; NSAID, nonsteroidal anti-inflammatory drugs; PD, probing depth; PI, plaque index; PISA, periodontal inflamed surface area; RA, rheumatoid arthritis; RCTs, randomized controlled clinical trials; RTX, rituximab; SSZ, sulfasalazine; TCZ, tocilizumab; tsDMARD, targeted synthetic DMARDs; TNF, tumor necrosis factor; TNFI, TNF inhibitor.

negligible effect on the periodontium in interventional studies with a longer follow-up (9 months and 15.1 months). However, the combination of tumor necrosis factor (TNF)-α inhibitors + methotrexate (MTX) was associated with a rise in gingival inflammation. Due to the considerable heterogeneity of the study designs, a meta-analysis could not reasonably be performed.

Conclusion: Within the limitations of the available studies, there is evidence to suggest that bDMARD monotherapy may improve the periodontal condition of RA patients with periodontal disease to a certain extent; the concomitant medication of TNF inhibitor + MTX could worsen gingival inflammation. More data are required to understand the impact of RA therapies on periodontal health.

KEYWORDS
antirheumatic agents, clinical studies, periodontal disease, periodontitis, rheumatoid arthritis

1 | INTRODUCTION

Periodontal diseases are biofilm-associated chronic inflammatory diseases affecting the tooth-supporting tissues (Pihlstrom et al., 2005). These diseases include gingivitis, with reversible damage of the superficial periodontium, and periodontitis, which leads to irreversible destruction of the superficial and deep periodontium, including fibrous attachment and supporting alveolar bone. Periodontitis has a high prevalence worldwide, affecting over half of the population and showing an increasing prevalence with age (Kassebaum et al., 2014). In periodontitis, an imbalanced relationship between an altered immune response and a dysbiotic microbiome triggers local inflammation and tissue breakdown (Hajishengallis, 2022). Moreover, due to bacteremia and hematogenous spread of inflammatory mediators, periodontitis affects general health. Consequently, an association between periodontitis and various chronic systemic diseases, such as diabetes mellitus, cardiovascular diseases, or rheumatoid arthritis (RA), has been increasingly supported by scientific evidence (Genco & Sanz, 2020).

RA is a chronic autoimmune degenerative inflammatory disease primarily affecting the joints, with a global prevalence of 0.5%–1% and a female-to-male ratio of 3:1 (Silman & Pearson, 2002). Clinically, RA is a long-term condition characterized by inflammation of the synovial lining of joints, leading to progressive destruction of cartilage and an erosion of marginal bone leading to the clinical symptoms of pain and stiffness on the joints and ultimately disability. RA is also associated with systemic complications and increased mortality (Kim & Suh, 2020).

RA and periodontitis share several common features. They are multifactorial chronic diseases influenced by modifiable and non-modifiable risk factors, such as age, tobacco use, obesity, and genetic predisposition (Koziel & Potempa, 2022). Local chronic inflammation and elevated levels of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, or IL-6, are observed in both diseases (Kobayashi & Yoshie, 2015). Furthermore, increased levels of proteolytic enzymes like matrix metalloproteinases (MMPs) and activation of the receptor activator of nuclear factor kappa B ligand (RANK-L) pathway (de Pablo et al., 2009) contribute to osteoclast differentiation, immune cell infiltration (neutrophils, macrophages, and B and T-lymphocytes), and subsequent tissue damage.

Extensive research has explored the bidirectional association between RA and periodontitis, revealing that patients with RA are 2.27 times more likely to be edentulous and almost twice as likely to have periodontitis than subjects without RA (de Pablo et al., 2008). Furthermore, individuals with a history of periodontitis for more than 5 years were shown to have a 69% greater risk for RA (Qiao et al., 2020). Periodontitis has been shown to influence the severity of RA (Rodríguez-Lozano et al., 2019).

While there is no cure for RA, modern therapeutic approaches achieve excellent control of this disease. Treatment includes lifestyle modifications, analgesics, anti-inflammatory drugs (e.g., nonsteroidal anti-inflammatory drugs [NSAID] and glucocorticoids), and disease-modifying antirheumatic drugs (DMARD). NSAIDs and glucocorticoids exert general anti-inflammatory action, whereas DMARD act through various mechanisms. Conventional synthetic DMARDs (csDMARDs), including methotrexate (MTX), hydroxychloroquine (HCQ), leflunomide (LM), or sulfasalazine (SSZ), ultimately interfere with critical pathways in the inflammatory cascade. Biologic DMARDs (bDMARDs) are monoclonal antibodies that target specific molecules of the immune system, such as TNF-α, IL-6, IL-1β, IL-17, or B or T cell expressed molecules. Targeted synthetic DMARDs (tsDMARDs), like janus kinases (JAK) inhibitors, similarly have specific targets (Aletaha & Smolen, 2018). csDMARDs have been in use since the 1970s, and bDMARDs since the early 1990s, tsDMARDs received their first FDA approval in 2012, resulting in a relatively limited amount of scientific literature on this newer treatment class.

Over the last decades, there has been extensive work investigating the proteins and pathways targeted by these DMARDS in the context of periodontal disease. This work has used human samples along with in vitro and in vivo systems. The findings—of which several are

published in this journal—have significantly informed the pathogenesis of periodontal disease. Given the effect of antirheumatic treatments on immune and inflammatory metabolism, by studying patients under these treatments for RA, there is an opportunity to explore whether these treatments could also influence periodontal health and the progression of periodontitis.

Moreover, the oral effects of RA treatments are important for the RA patients who are at increased risk of periodontitis. Thus, there is "double benefit" to studying the oral effects of RA treatments: (1) RA treatments are multiple and act at different levels, their impact on the periodontium may vary and give rise to specific recommendations depending on the treatment chosen for the patient. (2) Given the similarities in disease pathogenesis there may be opportunity for repurposing RA treatments as an alternative to antibiotics as an adjunct to periodontitis treatment. Consequently, the aim of this systematic review was to evaluate the current evidence regarding the impact of RA treatment on clinical signs of periodontal inflammation and related biomarkers.

2 | METHODS

2.1 | Search strategy

This systematic review was conducted according to the PRISMA guidelines (Page et al., 2021). To identify relevant studies, four databases, PubMed/MEDLINE, Cochrane Library, Embase, and Web of Science online databases up to January 2023, were searched independently by two researchers (C.P and P.S). The following keywords were used in various combinations: "periodontitis" OR "periodontal disease(s)" OR "periodontal inflammation" OR "periodontal treatment" OR "periodontal inflammation biomarkers" AND "rheumatoid arthritis treatment," "rheumatoid arthritis therapy," "psoriatic arthritis treatment," "psoriatic arthritis therapy," "antirheumatic agent(s)," "antirheumatic drug(s)," "DMARDs," "methotrexate," "leflunomide," "NSAIDs," "glucocorticoids," "anti-TNF-α," "anti-B lymphocyte," "anti-B-cell," "JAK inhibitors," and "IL-6 receptor inhibitor." Each researcher independently selected and reviewed the articles for the inclusion criteria and made a joint decision in case of disagreement. A hand search was performed in the reference lists of publications that addressed the topic, likewise.

2.2 | Eligibility criteria

The following PICOS framework was used to compose the focused question:

- Participants: Adult patients aged 18 years or older with RA
- Intervention: Antirheumatic medication
- Control: Patients with RA either without antirheumatic medication or with different treatment types for RA
- Outcome measures: Surrogate parameters for periodontal disease, bleeding on probing (BOP), gingival index (GI), periodontal inflamed surface area (PISA), probing depth (PD), or clinical attachment loss (CAL).

To be eligible for inclusion in this systematic review, the study had to meet the following criteria:

- Original research conducted in humans, published in peer-reviewed journals
- Randomized controlled clinical trials (RCTs), non-RCTs, cross-sectional studies, longitudinal studies, cohort studies, and case–control studies
- Assessed at least some of the periodontitis outcome measures described above
- Studies were excluded from the systematic review if they were conducted in patients undergoing immunosuppressive treatment for another reason than RA (e.g., cancer, transplant, chronic kidney disease, …) or if they were conducted in patients undergoing periodontal treatment.

2.3 | Data collection

Data extraction was performed recording the following:

- Author and year of publication
- Ethnicity, age, gender distribution, and sample size
- Smoking status
- Number of teeth
- RA diagnostic classification
- RA disease activity scale
- Duration of RA since diagnosis
- Type of antirheumatic medication
- Follow-up period
- Definition criteria of periodontal disease
- Type of periodontal disease
- Surrogate periodontitis clinical measures (PD, CAL, BOP, GI, and plaque index [PI])
- Microbiological analysis of subgingival biofilm samples and periodontal biomarkers
- Change of periodontal surrogate parameters during antirheumatic medication
- Additional findings

2.4 | Quality assessment

Two researchers (C.P and P.S) evaluated the risk of bias independently, using the Newcastle Ottawa Quality Assessment Scale (Wells et al., 2014) for cross-sectional and case–control studies and the Joanna Briggs Institute (JBI) critical appraisal checklist for longitudinal studies (Pearson et al., 2015). Disagreements between the researchers were discussed until a consensus was reached. Quality assessments of studies included in this systematic review are reported in Tables S1–S3.

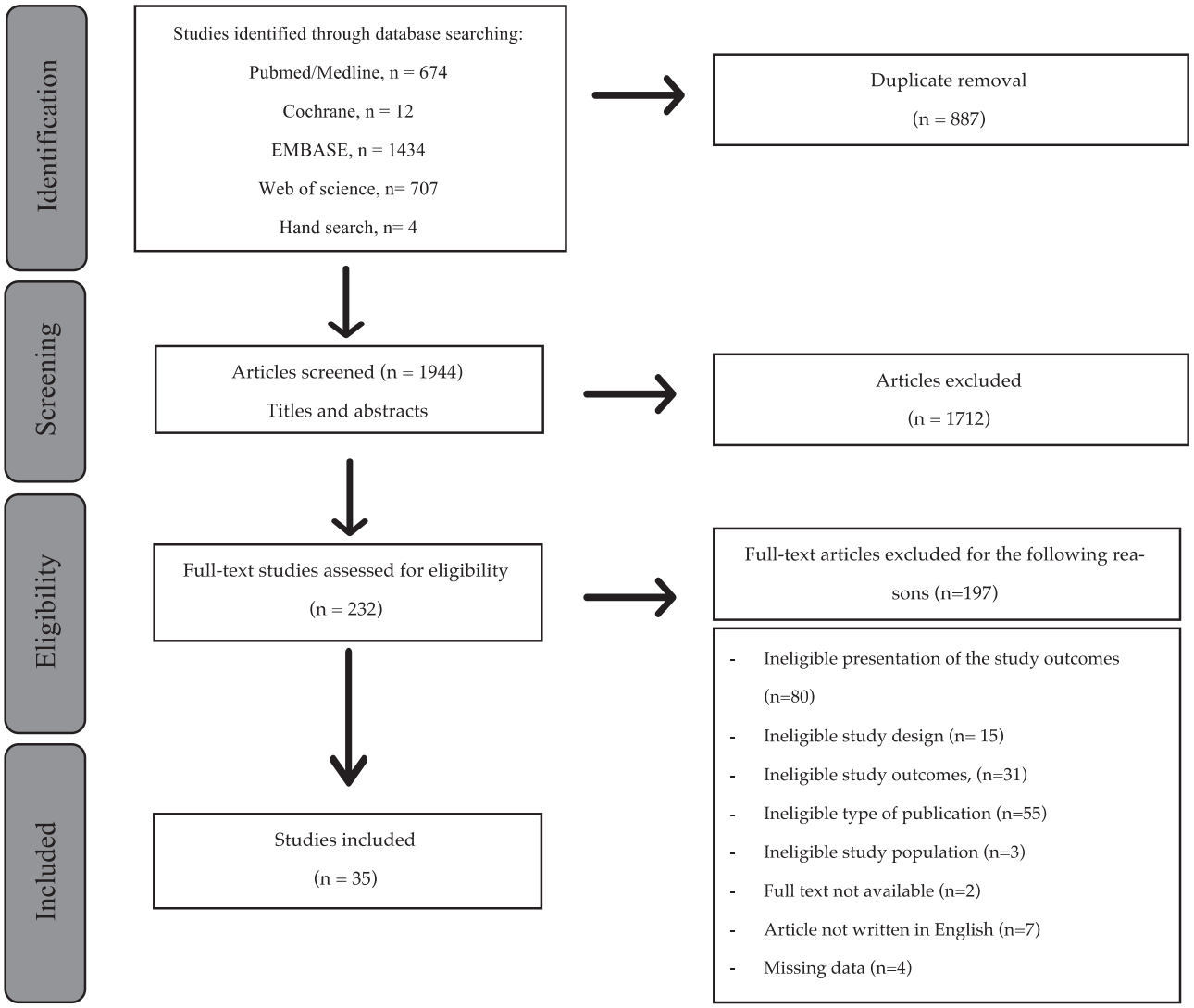

FIGURE 1 Flowchart showing PRISMA diagram for literature search and inclusion.

2.5 | Synthesis of the result

Data from the individual studies were merged qualitatively and, if feasable, quantitatively if the heterogeneity of the study designs allowed for reasonable comparison.

3 | RESULTS

3.1 | Study selection

The initial electronic search identified 2827 articles. The hand search revealed four further publications. A total of 887 duplicates were removed and then 1712 articles were excluded after screening of titles and abstracts. Finally, 232 full texts were considered for inclusion. Of these, 197 were excluded as they did not meet the criteria in Section 2.2. Studies were excluded as our required study outcomes were not available ($n = 80$), ineligible study design ($n = 15$), ineligible study outcomes based on our inclusion criteria ($n = 31$), ineligible type of publication ($n = 55$), ineligible study population ($n = 3$), full text not available ($n = 2$), article not written in English ($n = 7$), or missing data ($n = 4$). The list of full-text studies assessed for eligibility but excluded and reason for exclusion are reported in Table S4. Thirty-five studies were finally included in this systematic review. The selection process is depicted in Figure 1.

3.2 | Study characteristics

Among the 35 included studies published until January 2023, 19 are cross-sectional studies (Gamel et al., 2017; Hashimoto et al., 2021a, 2021b; Hatipoğlu et al., 2022; Jung et al., 2018; Kordtabar et al., 2019; Mayer et al., 2009, 2013; Mirrielees et al., 2010; Nik-Azis et al., 2021; Ortiz et al., 2009; Pischon et al., 2008; Renvert et al., 2020; Romero-Sanchez et al., 2017; Rovas et al., 2021; Schmalz et al., 2021; Wu et al., 2021; Yamashita et al., 2020; Ziebolz et al., 2018), 6 are case control

studies (Äyräväinen et al., 2017, 2018a, 2018b; de Smit et al., 2021; Kobayashi et al., 2015; Kobayashi, Okada et al., 2014); 8 are longitudinal studies (Ancuta et al., 2017, 2020, 2021; Fabri et al., 2015; Kadkhoda et al., 2016; Kobayashi, Yokoyama et al., 2014; Savioli et al., 2012; Üstün et al., 2013), and 2 are cross-sectional and longitudinal analyses in the one and the same article (Coat et al., 2015; Pers et al., 2008). All the studies were prospective except for one cross-sectional study (Yamashita et al., 2020). To date, no RCTs on the impact of RA treatment on periodontium have been published.

The sample sizes ranged from 6 to 862 patients with follow-up intervals ranging from 30 days to 15.9 ± 6.1 months. Age ranged from 18 to 87 years. Among the case–control studies, three articles reported on the same collective of patients. Thus, these three studies were considered one study in the present review (Äyräväinen et al., 2017, 2018a, 2018b).

A wide range of periodontal parameters were recorded in the individual studies, including clinical parameters like PD, CAL, PI, BOP, and GI, microbiological analysis of subgingival biofilm samples and laboratory data like gingival crevicular fluid (GCF) levels or salivary levels of MMP-8, TNF-α, MMP-3, IL-1β, IL-8, and monocyte chemoattractant protein-1 (MCP-1).

Due to considerable heterogeneity of the study designs, quantitative merging of the data was considered unreasonable.

Study characteristics based on the type of intervention are reported in Tables 1–3.

3.3 | Quality assessment

According to the Newcastle Ottawa Quality Assessment Scale, 6 of the cross-sectional studies were rated as fair quality (4–6), 15 of the cross-sectional studies were rated as good quality (7–10), and all the case–control studies were rated as good quality (7–10) (Tables S1 and S2). Looking at the longitudinal studies they satisfied from 5 to 7 of the 10 items of the JBI critical appraisal checklist for longitudinal studies (Table S3).

3.4 | Impact of the different anti RA drugs strategies on periodontal parameters

Identifying the impact of the myriad of different RA therapies on periodontal health is challenging. RA treatment may include combinations of different types of DMARDs. The following narrative attempts to delineate some of the RA therapies effects on periodontal health. The studies discussed are summarize in Tables 1–3; categorized according to study design (case control, cross-sectional, and longitudinal). The narrative attempts to provide a summary of the studies, according to medication type as this approach may be more informative to understanding mechanism and implications. The studies described below are predominantly cross sectional, comparing groups of patients treated with different drugs/different combinations of drugs.

3.4.1 | Impact of corticosteroids and NSAID on periodontal parameters

NSAIDs and corticosteroids were used (alone or in combination) as primary treatment for RA in two cross-sectional studies (Wu et al., 2021; Ziebolz et al., 2018). The authors found no intergroup differences in periodontal clinical parameters in term of PD, CAL, BOP, or PI. Combined NSAID and glucocorticoids were associated with the presence of *Treponema denticola* in dental plaque (Wu et al., 2021; Ziebolz et al., 2018).

NSAID and glucocorticoids were given as concomitant treatments with DMARDs in almost all other studies. In one cross-sectional study, patients taking corticosteroids alone had a lower GI (Nik-Azis et al., 2021). However, when NSAID and glucocorticoids were given as a co-medication, there was no impact on CAL (Gamel et al., 2017) or PD, PI, and BOP (Hashimoto et al., 2021b; Kordtabar et al., 2019; Renvert et al., 2020), or on salivary MMP-8 concentration (Äyräväinen et al., 2018b). Prednisolone intake was associated with fewer remaining teeth in RA patients ($p < 0.01$) in one cross-sectional study (Schmalz et al., 2021); however, another cross-sectional studies found an increase in the presence of teeth with steroid concomitant therapy (Romero-Sanchez et al., 2017). Two other cross-sectional studies found no change in tooth loss with corticosteroids and NSAIDs (Hashimoto et al., 2021b; Rovas et al., 2021).

3.4.2 | Impact of csDMARD on periodontal parameters

In a cross-sectional study comparing the effect of different csDMARDs on periodontitis, PD was significantly decreased in patients treated with MTX alone compared to other csDMARDs alone or in combination. There were no differences in any other periodontal clinical parameter (CAL, PI, GI, and BOP) in patients treated with HCQ only, SSZ only, or MTX + HCQ, or MTX + SSZ, or MTX + HCQ + SSZ (Jung et al., 2018). In a cross sectional study of newly diagnosed RA patients, there were no significant differences in the prevalence of periodontitis, or in PD, CAL, GI, or PI between patients with no RA treatment and RA patients on MTX or HCQ, with or without prednisolone or NSAID (Kordtabar et al., 2019). Similarly, A 2017 cross-sectional study found no significant correlation between the type of RA treatment (MTX, HCQ, SSZ, prednisolone, or NSAIDs) and CAL (Gamel et al., 2017).

Some cross-sectional studies have evaluated a variety of csDMARDS, alongside a group with a bDMARD. One such study found no differences in any periodontal clinical parameters (PI, BOP, GI, CAL, and PD) between patients treated with csDMARD and patients treated with TNF inhibitor (TNFI) (Romero-Sanchez et al., 2017). Within this study, a comparison of periodontal parameters in patients treated with different combination of csDMARD revealed an increase of sites with CAL ≥4 mm for patients treated with LM + MTX, compared to patients on MTX alone, or LM alone, or MTX + LM + SSZ, or MTX + HCQ (Romero-Sanchez et al., 2017).

TABLE 1 Summary of the included **cross-sectional studies** exploring the impact of antirheumatic treatment and medication time on periodontal status of patients with periodontal disease.

	Group I		Group II					
Authors, year of publication, country	Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	RA disease duration medication	Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	RA disease duration medication	Definition criteria of RA type of RA	Definition criteria of periodontal disease type of periodontal disease	Impact on periodontal conditions without periodontal treatment	Additional findings
Coat et al. (2015) France	10 63.2 ± 9.6 years 8/2 No smokers NR	15.4 ± 8.4 years RTX	11 60.8 ± 9.1 7/4 4 current smokers NR	13.00 ± 10.00 years MTX	1987 ACR classification criteria for RA NR	Update AAP/CDC 2012 Group I: 2 severe periodontitis, 8 moderate periodontitis, and 1 mild periodontitis Group II: 2 severe periodontitis, 3 moderate periodontitis and 4 mild periodontitis and 1 gingivitis	Better PD and CAL reduction and resolution of inflammation with RTX than with MTX	
Gamel et al. (2017) Sudan	57 42.9 ± 10.3 years 51/6 Only nonsmokers More than 10 teeth			NR PRED ($n = 40$), NSAID ($n = 5$) MTX ($n = 27$), HCQ ($n = 44$), SSZ ($n = 4$)	2010 RA classification criteria of ACR and EULAR NR	AAP 1999 chronic periodontitis	All groups are similar in term of CAL	
Hatipoğlu et al. (2022) Turkey	20 53.7 ± 10.19 16/4 Only no smokers NR	NR RTX	20 50.5 ± 11.3 16/4 Only no smokers NR	NR DMARD (but no RTX)	2010 RA classification criteria of ACR and EULAR Mean DAS score of 4.09 ± 0.99 for group I and 2.94 ± 1.14 for group II	AAP/EFP 2018 Healthy periodontium, $n = 7$/gingivitis, $n = 20$/Periodontitis, and $n = 43$	All groups are similar in term of PD, CAL, BOP, GI, and PI measures	GCF MMP8 level is lower in DMARD group GCF IL-1β level and GCF total volume are lower with RTX

(Continues)

TABLE 1 (Continued)

Authors, year of publication, country	Group I: Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	Group I: RA disease duration medication	Group II: Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	Group II: RA disease duration medication	Definition criteria of RA type of RA	Definition criteria of periodontal disease type of periodontal disease	Impact on periodontal conditions without periodontal treatment	Additional findings
Hashimoto et al. (2021b) Japan	94 62.0 (53.8, 73.3) 67/27 53 never smokers, 20 former smokers, and 21 current smokers At least one tooth			NR 3 groups: Group I = NSAIDs/ corticosteroid/ DMARDs Group II = MTX Group III = bDMARD	1987 ACR classification criteria for RA RA severity class I ($n = 65$) class II ($n = 17$), class III–IV ($n = 12$), RA severity stage I ($n = 56$), stage II ($n = 19$), stage III–IV ($n = 19$)	NR NR	All groups are similar in term of PD and tooth loss	Patients with more severe RA (class and stage) displayed a tendency towards bDMARD and MTX
Hashimoto et al. (2021a) Japan	74 62.7 ± 14.3 years 69/29 23 current smoker, 21 former smokers, and 54 never smokers 24.0 (16.8–27.3) teeth	25.5 (4.0 and 74.5) months DMARDs/ Corticosteroids/ NSAIDs/MTX	24 62.7 ± 14.3 years 69/29 23 current smoker, 21 former smokers, and 54 never smokers 24.0 (16.8–27.3)	36.0 (12.0, 66.0) months bDMARD	1987 ACR classification criteria for RA RA severity class I ($n = 68$) class II ($n = 17$), class III–IV ($n = 13$), RA severity stage I ($n = 60$), stage II ($n = 19$), and stage III–IV ($n = 19$)	NR NR	No significant association between the PISA score and the RA treatment	
Jung et al. (2018) Korea	32 62.0 ± 9.0 years 24/8 Two current smokers and 30 no smokers ≥20 teeth present			7.3 ± 6.1 years 5 groups : MTX ($n = 7$) HCQ ($n = 6$), MTX + HCQ ($n = 6$), MTX + SSZ ($n = 7$) MTX + SSZ + HCQ ($n = 6$)	1987 ACR classification criteria for RA Moderate or high disease activity (DAS28 ≥3.2)	Diagnosis of chronic periodontitis with at least five teeth with a CAL of ≥4 mm Chronic periodontitis	Patients on monoclonal MTX have lower PD All groups are similar in term of CAL and gingival inflammation	

(Continues)

TABLE 1 (Continued)

Authors, year of publication, country	Group I		Group II		Definition criteria of RA type of RA	Definition criteria of periodontal disease type of periodontal disease	Impact on periodontal conditions without periodontal treatment	Additional findings
	Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	RA disease duration medication	Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	RA disease duration medication				
Kordtabar et al. (2019) Iran	25 42.20 ± 10.84 22/3 No smokers ≥10 teeth	Between 6 weeks and 6 months None	25 40.72 ± 8.37 22/3 No smokers ≥10 teeth	More than 3 years MTX, HCQ, PRED, or NSAIDs	2010 RA classification criteria of ACR and EULAR Mean DAS28 score, $n = 4.03 \pm 1.53$ in group I and $n = 3.29 \pm 0.99$ in group II	AAP 1999 Chronic periodontitis	All groups are similar in term of periodontitis, or PD, CAL, GI, or PI	
Mayer et al. (2009) Israël	10 48.8 ± 13.64 years 5/5 3 current smokers NR	4.6 ± 2.12 years NSAID, glucocorticoids, and DMARD but no TNFI	10 51.9 ± 6.74 years 7/3 3 current smokers NR	16.4 ± 12.68 years Infliximab	1987 ACR classification criteria for RA NR	AAP 1999 25 patients (83%) had moderate-advanced chronic periodontitis, 4 (13%) had slight chronic periodontitis, and 1 (3%) had gingivitis	CAL, GI, and BOP are significantly lower in patients on infliximab Both groups are similar in term of PI	TNF-α in GCF is significantly lower in patients on infliximab
Mayer et al. (2013) Israël	12 48.2 ± 12.0 years 7/5 16.6% current smokers NR	5.0 ± 2.1 years Any RA treatment (NR) but TNFI	10 53.6 ± 6.2 years 7/3 30% current smokers NR	16.3 ± 14 years Infliximab	1987 ACR classification criteria for RA	NR 79% had moderate to severe chronic periodontitis, 16% had slight periodontitis, and 5% had gingivitis	Patients under infliximab have lower CAL, lower PI, and less inflammation (better BOP and GI) than patients under other RA treatment All groups are similar in term of PD or tooth loss	TNF-α in GCF is significantly lower in patients on infliximab

(Continues)

TABLE 1 (Continued)

Authors, year of publication, country	Group I		Group II		Definition criteria of RA type of RA	Definition criteria of periodontal disease type of periodontal disease	Impact on periodontal conditions without periodontal treatment	Additional findings
	Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	RA disease duration medication	Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	RA disease duration medication				
Mirrielees et al. (2010) Kentucky, USA	35 46.8+/−10.5 years 77.2% f/22.8% m 11.4% current smokers ≥18 erupted teeth			At least 3 years Four groups of treatment: - Monoclonal TNFI - MTX - LM with MTX, HCQ, or Monoclonal TNFI - No DMARDs	1987 ACR classification criteria for RA NR	AAP 1999 Chronic adult periodontitis	All groups are similar in term of PD, CAL, tooth loss, and BOP	IL-1β salivary level is significantly lower in patients on monoclonal anti-TNF-α However, all groups are similar in term of salivary level of MMP-8 or TNF-α
Nik-Azis et al. (2021) Malaysia	130 56.6 years 119 women and 11 men 3 current smokers, 5 former smokers, and 122 never smokers 22 (14.00–26.00) teeth			Mean RA disease duration was between 10.54 ± 8.58 years (combination of more than one DMARD) and 16.63 ± 18.35 years (SSZ) Six groups: - MTX ($n = 37$) - HCQ ($n = 4$) - SSZ ($n = 8$), - LM ($n = 3$) - Cmbination of more than one DMARD ($n = 57$) - No DMARD ($n = 20$)	2010 RA classification criteria of ACR and EULAR Mean DAS28 = 3,43.32 ±	AAP/EFP 2018 92 periodontitis, 6 gingivitis, and 31 periodontally healthy patients	All groups are similar in term of PD, CAL, PI, and GI When comparing patients on monoclonal MTX VS patients on combination of MTX + other DMARD, subjects on a combination of MTX + DMARDs have higher stage of periodontitis, deeper PD, deeper CAL, and higher PI than patients on monoclonal MTX GI is significantly lower in subjects taking corticosteroids	

(Continues)

TABLE 1 (Continued)

Authors, year of publication, country	Group I		Group II		Definition criteria of RA type of RA	Definition criteria of periodontal disease type of periodontal disease	Impact on periodontal conditions without periodontal treatment	Additional findings
	Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	RA disease duration medication	Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	RA disease duration medication				
Ortiz et al., 2009 Ohio, USA	20 55.5 [39–87] years 18/2 No smokers only ≥20 teeth	NR MTX, HCQ, LM, or SSZ	20 55.5 [39–87] years 17/3 No smokers only ≥20 teeth	NR TNFI	NR Moderate to severe RA	NR Severe periodontitis	Both groups are similar in term of PD, CAL, BOP, GI, and PI	Both groups are similar in term of mean serum TNF-α level
Pers et al. (2008) France	20 53.2 ± 8.2 years [34–71] 16/4 Five current smokers DMFT: 18.51 ± 4.01	NR infliximab	20 55.4 ± 12.0 years [31–76] 15/5 Four current smokers DMFT: 17.02 ± 4.44	NR MTX	1987 ACR classification criteria for RA Mean DAS 28 score at baseline = 343	NR NR	Subjects on infliximab have more inflammation (worst MGI and PBI) than patients on monoclonal MTX	All subjects on infliximab had concomitant MTX treatment
Pischon et al. (2008) Germany	57 52.1 ± 13.0 years 49/8 12 current smokers, 22 former smokers, and 23 never smokers NR			Median disease duration is 10.5 years Corticosteroids, TNFI, DMARDs, and NSAIDs	1987 ACR classification criteria for RA DAS28 mean score was 3.40 (2.50–5.10) for patients with CAL ≤4 mm and 3.15 (2.70–4.70) for patients with CAL > 4 mm	Periodontal disease was defined as a mean CAL > 4.0, corresponding to the median level in included population	All groups are similar in term of the onset and severity of periodontitis according to the definition of periodontitis chosen in this study	

(Continues)

TABLE 1 (Continued)

Authors, year of publication, country	Group I: Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	Group I: RA disease duration medication	Group II: Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	Group II: RA disease duration medication	Definition criteria of RA type of RA	Definition criteria of periodontal disease type of periodontal disease	Impact on periodontal conditions without periodontal treatment	Additional findings
Renvert et al. (2020) Sweden	126 70 ± 6.6 years 70% f/30% m 61.9% of current-past smokers ≥10 teeth			14 ± 13 years csDMARDs (66%), MTX (57%), bDMARD (22%), and glucocorticoids (45%)	2010 RA classification criteria of the ACR and EULAR And 1987 ACR classification criteria for RA A majority of the individuals in the RA group (63%) were in remission or diagnosed as having low disease activity	Gingivitis was defined as having ≥20% of measured sites with evidence of bleeding on probing. Periodontitis was defined as the clinical presence of bleeding on probing at >20% of recorded tooth surfaces, presence of >2 non-adjacent sites with a probing pocket depth (PPD) ≥5 mm, presence of bone loss at ≥2 sites with a distance between cement enamel junction-to bone level of ≥5 mm, or if evidence of a furcation invasion at molar teeth was found either clinically (grade II), or clearly visible on panoramic radiographs All type of periodontal disease	All groups are similar in term of PD, PI, BOP, and radiographic extent of alveolar bone loss	

(Continues)

TABLE 1 (Continued)

Authors, year of publication, country	Group I		Group II		Definition criteria of RA type of RA	Definition criteria of periodontal disease type of periodontal disease	Impact on periodontal conditions without periodontal treatment	Additional findings
	Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	RA disease duration medication	Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	RA disease duration medication				
Romero-Sanchez et al. (2017) Colombia	115 55.85 ± 8.97 years 80.87% f/19.13% m 2.86% of current smokers, 40.78% of former smokers, 13.46% of passive smokers Mean 1.89 ± 0.70 teeth	csDMARD: - MTX alone - LM alone - LM + MTX - MTX + HCQ - MTX + SSZ	62 55.20 ± 9.72 years 79.66% f/20.34% m 5.36% of current smokers, 26.79% of former smokers, 8.93% of passive smokers Mean 1.92 ± 0.78 teeth	TNFI: - TNFI alone - TNFI + MTX - TNFI + LM	2010 RA classification criteria of ACR and EULAR And 1987 ACR classification criteria for RA All type of RA activity: - Group I mean DAS28 = 3.05 ± 1.26 - Group II mean DAS28 = 3.49 ± 1.56	Update AAP/CDC 2012 All type of periodontal disease Frequency of periodontal disease: - 88.7% in group I (csDMARD) - 93.22% in group II (TNFI)	Both groups are similar in term of PI, BOP, GI, CAL, PD. When looking to subgroups of patients on csDMARD, % of sites with CAL ≥4 mm is significantly associated with MTX + LM. Regarding subgroups of patients on TNFI, TNFI + MTX is associated with lower extension of interproximal sites with CAL≥4 mm.	*T. denticola* is significantly increased in TNFI group. *T. forsythia* is significantly increased in monoclonal TNFI subgroup. *P. gingivalis* and *E. nodatum* are significantly associated with the use of more than one DMARD Steroid concomitant therapy was associated with the presence of teeth
Rovas et al. (2021) Lithuania	64 55.5 ± 9.57 years 55/9 15 current smokers, 12 former smokers, and 37 never smokers NR		11.47 ± 8.59 years 26 patients treated with bDMARD 38 patients treated without bDMARD		2010 RA classification criteria of ACR and EULAR All type of RA activity	AAP/EFP 2018 Periodontitis	Patients on bDMARDs have lower BOP All groups are similar in term of CAL, PD, bone loss, and number of missing teeth	
Schmalz et al. (2021) Germany	101 57.48 ± 10.03 82/19 20 current smokers, 81 nonsmokers 22.85 ± 4.26 teeth		6.60 ± 8.49 years Prednisolone, methotrexate, and bDMARD		2010 RA classification criteria of ACR and EULAR DAS28-ESR : 3.44 ± 1.42	AAP/EFP 2018 Periodontitis only (0 stage I, 9 stage II, 46 stage III, 46 stage IV, 81 grade B and 20 grade C)	There is no association between PISA and RA medication	Prednisolone is associated with a lower number of remaining teeth

(Continues)

TABLE 1 (Continued)

Authors, year of publication, country	Group I		Group II		Definition criteria of RA type of RA	Definition criteria of periodontal disease type of periodontal disease	Impact on periodontal conditions without periodontal treatment	Additional findings
	Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	RA disease duration medication	Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	RA disease duration medication				
Wu et al. (2021) China	862 18 ± 65 years 658/204 180 smokers Mean missing teeth: 3.26 ± 0.24			NR 7 subgroups: - NSAID + gluco-corticoids, *n* = 135 - MTX, *n* = 115 - LM, *n* = 117 - MTX + TNFI, *n* = 121 - IL-6 antagonist, *n* = 123 - MTX + RTX, *n* = 122 - DMARD in combination, *n* = 129	2010 RA classification criteria of ACR and EULAR	CPITN all type of periodontal status	All groups are similar in term of PD, CAL, and tooth loss However, PBI was higher in patients on MTX + TNFI PBI was significantly lower with LM	*P.g* is significantly increased with monoclonal LM and MTX + TNFI *T.f* is decreased with MTX + RTX *T.d* is increased with NSAID + gluco-corticoids, monoclonal MTX, or monoclonal LM
Yamashita et al. (2020) Japan	27 52.9 ± 12.7 years 24/3 15% former smokers and 85% never smokers 25.1 ± 4.0 teeth	75.1 ± 82.4 months TNFI (4 infliximab, 5 etanercept, 9 adalimumab, and 3 golimumab)	27 57.7 ± 10.5 years 25/2 11% former smokers and 89% never smokers 24.9 ± 4.6 teeth	83.5 ± 74.0 months TNFI (2 infliximab, 4 etanercept, 7 adalimumab, and 2 golimumab)	2010 RA classification criteria of ACR and EULAR DAS28 average of 3.9	Update AAP/CDC 2012 - No periodontitis: *n* = 0 in group I, *n* = 9% in group II - Mild periodontitis: *n* = 45% in group I, *n* = 48%% in group II - Moderate periodontitis: *n* = 33% in group I, *n* = 28% in group II - Severe periodontitis: *n* = 22% in group I, *n* = 15% in group II	TNFI had no impact on PISA level	

(Continues)

TABLE 1 (Continued)

Authors, year of publication, country	Group I: Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	Group I: RA disease duration medication	Group II: Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	Group II: RA disease duration medication	Definition criteria of RA type of RA	Definition criteria of periodontal disease type of periodontal disease	Impact on periodontal conditions without periodontal treatment	Additional findings
Ziebolz et al. (2018) Germany	168 58.5 ± 10 years 137/31 43 current smokers Mean missing teeth: 6.05 ± 4.80 teeth			NR Seven subgroups depending on the mediaction: - Gr1: NSAID and glucocorticoids, *n* = 17, - Gr2: MTX, *n* = 41, - Gr3: LM, *n* = 28, - Gr4: MTX + TNFI, *n* = 27, - Gr5: IL-6 antagonist, *n* = 16, - Gr6: MTX + RTX, *n* = 19 - Gr7: combined DMARDs, *n* = 20	1987 ACR classification criteria for RA Mean DAS28-ESR score at baseline: - 3.60 ± 1.81 (gr I) - 3.29 ± 1.27 (gr II) - 3.67 ± 1.38 (gr III) - 3.15 ± 1.22 (gr IV) - 3.87 ± 1.43 (gr V) - 3.67 ± 1.48 (gr VI) - 3.72 ± 1.32 (gr VII)	AAP/CDC 2007 All type of periodontal status: no or mild periodontitis/moderate periodontitis and severe periodontitis	All groups are similar in term of PD and CAL However, PBI and BOP are higher with MTX + TNFI compared with LM or with MTX + RTX	*P.g* is associated with LM *T.d* is associated with NSAID + glucocorticoids and monoclonal MTX *F.n* is decreased with MTX + RTX *Capnocytophaga* species are associated with IL-6 antagonists

Abbreviations: AAP, American Academy of Periodontology; ACR, American College of Rheumatology; bDMARD, biologic DMARD; BoP, bleeding on probing; CAL, clinical attachment level; CDC, Centers for Disease Control and Prevention; csDMARD, convensional synthetic DMARD; DAS, disease activity score; DAS28-ESR, disease activity score on 28 evaluable joints using erythrocyte sedimentation rate; DMARD, disease modifying antirheumatic drugs; EFP, European Federation of Periodontology; EULAR, European League Against Rheumatism; F.n, *Fusobacterium nucleatum*; f/m, proportion of female and male patients; GCF, gingival crevicular fluid; GI, gingival index; HCQ, hydroxychloroquine; IL-1β, interleukine 1bêta; IL-6, interleukine 6; LM, leflunomide; MGI, modified gingival index; MMP-8, metalloproteinase 8; MTX, methotrexate; NR, not reported; NSAID, nonsteroidal anti-inflammatory drugs; P.g, *Porphyromonas gingivalis*; PBI, papilla bleeding index; PD, pocket depth; PI, plaque index; PISA, periodontal inflamed surface area; PRED, prednisolone; RA, rheumatoid arthritis; RTX, rituximab; RTX, rituximab; SSZ, sulfasalazine; *T.d*, *Treponema denticola*; T.f, *Tannerella forsythia*; TNF-α, tumor necrosis factor alpha; TNFI, tumor necrosis factor inhibitor.

Source: AAP 1999, 1999 International Workshop for a Classification of Periodontal Diseases and Conditions conducted by the American Academy of Periodontology.

AAP/CDC 2007, Case Definitions for Use in Population-Based Surveillance of Periodontitis supported by the Centers for Disease Control and Prevention (CDC), in partnership with the American Academy of Periodontology (AAP).

Update AAP/CDC 2012, update of the case definitions for periodontitis supported by the Centers for Disease Control and Prevention (CDC), in partnership with the American Academy of Periodontology (AAP), by Eke et al. (2012).

AAP/EFP 2018, American Academy of Periodontology/European Federation of Periodontology classification of periodontal and peri-implant diseases and conditions, Chicago 2018.

TABLE 2 Summary of **case control studies** exploring the impact of different antirheumatic treatment on periodontal tissues.

Authors, year of publication, country	Group I: Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	Group I: RA disease duration name of drug	Group II: Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	Group II: RA disease duration name of drug	Follow-up	Definition criteria of RA type of RA	Definition criteria of periodontal disease type of periodontal disease	Impact on periodontal conditions without periodontal treatment (intragroup effect): Group	PD	CAL	PI	GI	BOP/PISA	Perio Biomarkers or pathogens	Additional findings (intergroup effect)
Kobayashi, Okada et al. (2014) Japan	28 60.3 ± 1.9 22/6 Current, former and never smokers 24.6 ± 0.6 teeth	162.5 ± 21.2 months TCZ	27 61.9 ± 2.1 years 22/5 Current, former and never smokers 23.1 ± 0.9 teeth	155.0 ± 31.3 months Corticosteroids (n = 13), DMARDs (n = 16), and NSAID (n = 1)	8 weeks	1987 ACR classification criteria for RA - Remission: 7 in group I and 14 in group II - Low disease activity: nine in group I and four in group II - Moderate disease activity: 11 in group I and 8 in group II - High disease activity: 1 in group I and 1 in group II	AAP 1999 Slight to moderate periodontitis	Gp I Gp II	↓ NS	↓ NS	NS NS	↓ NS	↓ NS	↓MMP-3 ↓IL-6 NS	At follow-up, GI, %BOP, serum level of MMP-3 and GCF level of MMP-3 are significantly lowered with TCZ Patient on TCZ have a significant greater decrease in GI, BOP, PD, CAL, %sites with PD 4–6 mm, %sites with CAL 4–6 mm and serum level of MMP-3 and IL-6 than patients on DMARD and/or steroids
de Smit et al. (2021) Netherlands	14 61 [49–66] 71% f/29% 21% current smokers 26 [24–29] teeth	Median RA disease duration: 19 months [6–370 months] MTX	12 64 [57—67] 75% f/25% m 17% current smokers 25 [23–27] teeth	median RA disease duration: 19 months [6—370 months] TNFI + MTX	>2months	2010 RA classification criteria of ACR and EULAR Mean DAS28-ESR at baseline, n = 5.8 [3.8–6.5] in group I, and n = 5.3 [4.2–5.8] in group II	Update AAP/CDC 2012 Gingivitis, moderate periodontitis, severe periodontitis	Gp I Gp II	NS NS	- -	NS NS	- -	NS NS	- -	Both groups are similar in term of PD, BOP, PISA, FMPS, and number of teeth at baseline and after 2 months of follow-up

(Continues)

TABLE 2 (Continued)

Authors, year of publication, country	Group I: Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	Group I: RA disease duration name of drug	Group II: Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	Group II: RA disease duration name of drug	Follow-up	Definition criteria of RA type of RA	Definition criteria of periodontal disease type of periodontal disease	Impact on periodontal conditions without periodontal treatment (intragroup effect)							Additional findings (intergroup effect)
								Group	PD	CAL	PI	GI	BOP/PISA	Perio Biomarkers or pathogens	
Kobayashi et al. (2015) Japan	20 54.5 ± 11.8 19/1 1 former smoker and 19 never smokers ≥15 teeth	75.3 ± 74.4 TCZ	40 56.4 ± 11.3 35/5 4 former smokers and 36 never smokers ≥15 teeth	79.6 ± 77.1 TNFI (6 cases of infliximab, 9 cases of etanercept, 19 cases of a humanized anti-TNF-α monoclonal antibody, and 6 cases of golimumab)	6 months	2010 RA classification criteria of ACR and EULAR - Remission: $n = 1$ in group test, $n = 3$ in group control - Low disease activity: $n = 2$ in group test, $n = 2$ in group control - Moderate disease activity: $n = 10$ in group test, $n = 20$ in group control - High disease activity: $n = 7$ in group test, $n = 15$ in group control	Periodontitis was determined by the presence of sites with CAL ≥4 mm Periodontitis	Gp I	↓	↓	NS	↓	↓	MMP-3↓ TNF-α ↓ IL-6 NS	At follow-up, GI decrease is bigger with TCZ
								Gp II	↓	NS	NS	↓	↓	MMP-3↓	Both groups are similar in term of PD, CAL, and PI At follow-up both groups displayed a significant decrease in serum levels of MMP-3

(Continues)

TABLE 2 (Continued)

Authors, year of publication, country	Group I: Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	Group I: RA disease duration name of drug	Group II: Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	Group II: RA disease duration name of drug	Follow-up	Definition criteria of RA type of RA	Definition criteria of periodontal disease type of periodontal disease	Impact on periodontal conditions without periodontal treatment (intragroup effect): Group	PD	CAL	PI	GI	BOP/PISA	Perio Biomarkers or pathogens	Additional findings (intergroup effect)
Äyräväinen et al. (2017, 2018a, 2018b) Finland	53 51 ± 15 years 85% f/15% m 11 current smokers, 7 former smokers, and 35 never smokers NR	10.4 ± 17.1 months csDMARDs (MTX, LM, SSZ, HCQ)	28 52 ± 11 years 82% f/18% m 3 current smokers, 2 former smokers, and 23 never smokers NR	176 ± 116.8 months bDMARD (TNFI or non-TNFI	15.9 ± 6.1 months	1987 ACR classification criteria for RA Moderate or high disease activity (DAS ≥ 3.2) of RA was present in 69.8% of the ERA and in 67.8% of the CRA patients	AAP/CDC 2007 67% of the patients in group I and 64% of the patients in group II had moderate periodontitis at baseline	Gp I Gp II	NS NS	NS NS	NS NS	– –	NS NS	MMP-8 NS MMP-8 NS	Both groups are similar in term of PD, CAL, PI, BOP, and salivary IL-6, MMP-8, and TIMP-1 concentration at follow-up

Abbreviations: AAP, American Academy of Periodontology; ACR, American College of Rheumatology; BoP, bleeding on probing; CAL, clinical attachment level; CDC, Centers for Disease Control and Prevention; DAS, disease activity score; DAS28, disease activity score on 28 evaluable joints; DAS28-ESR, disease activity score on 28 evaluable joints using erythrocyte sedimentation rate; DMARD, disease modifying antirheumatic drugs; EULAR, European League Against Rheumatism; FMPS, full mouth plaque score; GCF, gingival crevicular fluid; GI, gingival index; Gp I, group I; Gp II, group II; HCQ, hydroxychloroquine; IL-1β, interleukine 1bêta; IL-6, interleukine 6; IL-8, Interleukine 8; LM, leflunomide; MCP-1, monocyte chemoattractant protein-1; MMP-3, metalloproteinase 3; MMP-8, metalloproteinase 8; MTX, methotrexate; NR, not reported; NS, not statistically significant; NSAIDs, non steroidal anti-inflammatory drugs; PD, pocket depth; PI, plaque index; PISA, periodontal inflamed surface area; RA, rheumatoid arthritis; SSZ, sulfasalazine; TCZ, tocilizumab; TIMP-1, tissue inhibitor of MMPs 1; TNFI, tumor necrosis factor inhibitor.

Source: AAP 1999, 1999 International Workshop for a Classification of Periodontal Diseases and Conditions conducted by the American Academy of Periodontology.

AAP/CDC 2007, Case Definitions for Use in Population-Based Surveillance of Periodontitis supported by the Centers for Disease Control and Prevention (CDC), in partnership with the American Academy of Periodontology (AAP).

Update AAP/CDC 2012, update of the case definitions for periodontitis supported by the Centers for Disease Control and Prevention (CDC), in partnership with the American Academy of Periodontology (AAP), by Eke et al. (2012).

Legend: Green arrow (↑↓) = significant improvement, red arrow (↑↓) = significant worsening.

TABLE 3 Summary of the included **longitudinal studies** exploring the impact of different antirheumatic treatment on periodontal tissues.

Authors, year of publication, country	Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	Name of antirheumatic drug	Duration of RA (mean disease duration ± SD)	Follow-up	Definition criteria of RA type of RA	Definition criteria of periodontal disease type of periodontal disease	Impact on periodontal conditions without periodontal treatment					
							PD	CAL	PI	GI	BOP	Periodontal biomarkers
Üstün et al. (2013) Turkey	16 34.80 ± 8.01 years 7/9 Only no smokers ≥1 tooth	TNFI (adalimumab and infliximab)	3.62 ± 2.24 years	30 days	1987 ACR classification criteria for RA DAS28 at baseline: 5.07 ± 0.66	AAP 1999 Group I suffers from chronic periodontitis, Group II has no periodontal disease	NS	NS	NS	↑	↑	IL-1β↓ IL-8↓ MCP-1↓ GCF ↓
Kadkhoda et al. (2016) Iran	36 40.8 ± 12.3 years 26/10 NR ≥6 Ramfjord's teeth	Altebrel (=Etanercept)	NR	6 weeks	2010 RA classification criteria of ACR and EULAR NR	Generalized inflammation ± PD ≥5 mm All type of periodontal disease	NS	–	NS	↓	↓	↓ GCF- level of TNF-α
Kobayashi, Yokoyama et al. (2014) Japan	20 51.7 ± 2.2 years 1/19 0 current smokers, 3 former smokers, 17 never smokers 26.6 ± 0.5 teeth	Adalimumab	108.6 ± 24.4 months	3 months	1987 ACR classification criteria for RA 2010 RA classification criteria of ACR and EULAR 2 remission, 1 low activity, 10 moderate activity, and 7 high activity	NR NR	↓	NS	NS	↓	↓	↓ serum- level of MMP-3 ↓ serum- level of IL-6 ↓ serum- level of TNF-α
Ancuța et al. (2020) Romania	21 60.00 years [53.25 ± 64.5] 18/3 Exclusion of current smokers At least 8 evaluable teeth	Baricitinib	117.16 months [49.25 ± 159.00]	24 weeks	2010 RA classification criteria of ACR and EULAR Moderate to severe active disease	AAP/EFP 2018 All type of periodontal status (healthy, gingivitis, and periodontitis)	↓	NS	NS	↓	↓	–
Savioli et al. (2012) Brazil	18 median age: 50 years [25–71] 94,4% f/5.6% m 25% of current smokers	Infliximab, adalimumab and etanercept	10.5 years [2–43]	6 months	1987 ACR classification criteria for RA Mean DAS28 score at baseline: 5.5 [4.0–6.2]	AAP 1999 Mild or moderate periodontitis (8 patients) versus no periodontitis (10 patients)	NS	NS	↓	NS	–	–

(Continues)

TABLE 3 (Continued)

Authors, year of publication, country	Sample size, age (year), gender distribution (f/m), smoking status, number of teeth	Name of antirheumatic drug	Duration of RA (mean disease duration ± SD)	Follow-up	Definition criteria of RA type of RA	Definition criteria of periodontal disease type of periodontal disease	Impact on periodontal conditions without periodontal treatment					
							PD	CAL	PI	GI	BOP	Periodontal biomarkers
Coat et al. (2015) France	11 60.8 ± 9.1 years 7/4 4 current smokers, 7 nonsmokers NR	Rituximab	13.00 ± 10.00 years	6 months	1987 ACR classification criteria for RA 2 severe periodontitis, 8 moderate periodontitis, and 1 mild periodontitis	Update AAP/CDC 2012 2 severe periodontitis + 8 moderate periodontitis + 1 mild periodontitis	↓	↓	NS	NS	–	–
Fabri et al. (2015) Brazil	15 48.6 ± 11.6 years 7% of men NR At least 8 teeth	TNFI (infliximab (80%), adalimumab (14%), and etanercept (6%)	14.1 ± 10.0 years	6 months	1987 ACR classification criteria for RA NR	AAP 1999 Mild periodontitis	NS	NS	NS	–	NS	–
Ancuta et al. (2017) Romania	96 49.2 ± 25.7 years NR Never smokers only 23.7 ± 9.7 teeth	TNFI	56.5 ± 32.1 months	6 months	NR Moderate-to-severe disease activity	NR NR	↓	↓	NS	NS	↓	–
Ancuța et al. (2021) Romania	51 56.3 ± 15.7 years 46/5 Never smokers only 23.7 ± 3.4 teeth	TCZ	81.3 ± 68.9 months	6 months	1987 ACR classification criteria for RA AND 2010 RA classification criteria of the American college of rheumatology and EULAR Moderate-to-severe disease activity	NR All type of periodontal disease (gingivitis or periodontitis)	↓	↓	NS	↓	↓	–
Pers et al. (2008) France	9 52,88 years [34–67] 7/2 2 current smokers NR	Infliximab	NR	Up to 9 months	1987 ACR classification criteria for RA Mean DAS 28 score at baseline: 343 [1.06–5.99]	NR NR	NS	↓	NS	↑	↑	–

Abbreviations: AAP, American Academy of Periodontology; ACR, American College of Rheumatology; BoP, bleeding on probing; CAL, clinical attachment level; CDC, Centers for Disease Control and Prevention; EFP, European Federation of Periodontology; EULAR, European League Against Rheumatism; GCF, gingival crevicular fluid; GI, gingival index; IL-6, interleukine 6; MMP-3, metalloproteinase 3; NR, not reported; NS, not statistically significant; PD, pocket depth; PI, plaque index; RA, rheumatoid arthritis; TNF-α, tumor necrosis factor alpha; TNFI, tumor necrosis factor inhibitor.

Source: AAP 1999, 1999 International Workshop for a Classification of Periodontal Diseases and Conditions conducted by the American Academy of Periodontology.

Update AAP/CDC 2012, update of the case definitions for periodontitis supported by the Centers for Disease Control and Prevention (CDC), in partnership with the American Academy of Periodontology (AAP), by Eke et al. (2012).

AAP/EFP 2018, American Academy of Periodontology/European Federation of Periodontology classification of periodontal and peri-implant diseases and conditions, Chicago 2018.

Legend: Green arrow (↓↓) = significant improvement, red arrow (↑↓) = significant worsening.

In another cross-sectional study, RA treatment with MTX alone, or LM in combination with one of either MTX, or HCQ, or TNFI or TNFI alone, or no DMARD had no impact on PD, CAL, tooth loss, and BOP (Mirrielees et al., 2010).

With regard to periodontal key pathogens, MTX was associated with an increase of *T. denticola*, whereas LM was associated with an increase of *Porphyromonas gingivalis* in two studies (Wu et al., 2021; Ziebolz et al., 2018) as compared to NSAID + glucocorticoids or IL-6 antagonist or combined MTX + TNFI or MTX + rituximab (RTX) or other DMARD in combination.

3.4.3 | Impact of biologic DMARD (bDMARD) on periodontal parameters

A group of Finnish authors published three articles based on the same prospective cohort. These studies found no significant difference between treatment with csDMARD and bDMARD in terms of BOP, PIBI, mean PD, number of PD≥4 mm, mean CAL, and salivary Il-6 and MMP-8 level after 15.9 ± 6.1 months of treatment (Äyräväinen et al., 2017, 2018a, 2018b). One recent prospective study found no significant differences between group I on MTX and group II on TNFTNFI + MTX in term of PI, PD, and inflammation after 2 months of follow-up (de Smit et al., 2021).

Patients treated with RTX had better periodontal clinical parameters with lower level of PD, CAL, PI, and MGI than patients treated with MTX (Coat et al., 2015). Another study found no association between the PISA score and the type of RA treatment (csDMARD, or bDMARD, or NSAID/corticosteroids) (Hashimoto et al., 2021a). The same authors found no impact of RA treatment (NSAID, or MTX, or bDMARD, or other DMARD) on PD or tooth loss (Hashimoto et al., 2021b). Another group found no significant differences in periodontal parameters between patients on csDMARD and patients on TNFI (Ortiz et al., 2009). No differences were found in another cross-sectional study regarding PD, PI, BOP, and radiographic bone loss (BL) between the patients on csDMARD and patients on bDMARD (Renvert et al., 2020).

Some studies suggest that the use of bDMARDs was associated with a lower BOP. However, there was no significant differences in CAL, PD, BL, and number of missing teeth among patients treated with bDMARDs as compared to patients without bDMARDs (Rovas et al., 2021). Four studies that assessed the impact of bDMARD versus MTX versus glucocorticoid on periodontal tissue found no impact of medication on the PISA (Hashimoto et al., 2021a; Schmalz et al., 2021), on PD and tooth loss (Hashimoto et al., 2021b) or on any other periodontal clinical parameter (Renvert et al., 2020). Three articles based on the same study design and patient groups found no differences in periodontal parameters or on salivary levels of MMP-8, IL-6, and TIMP-1 in RA patients with bDMARD versus csDMARD (Äyräväinen et al., 2017, 2018a, 2018b).

Finally, a cross-sectional study reported that patients on MTX or bDMARD are more likely to have less teeth than patients on NSAID or corticoids or other DMARDs (Hashimoto et al., 2021b).

The periodontal effects of some bDMARDS have been evaluated longitudinally; usually by evaluating periodontal parameters before and after treatment with the bDMARD. Some studies include comparisons with concomitant bDMARD and periodontal treatment.

Anti-TNF drugs (etanercept, adalimumab, infliximab; TNFI–TNF inhibitors)

A longitudinal study reported a beneficial effect on periodontal inflammation after only 6 weeks of etanercept treatment (Kadkhoda et al., 2016). In two other longitudinal studies conducted by the same team, authors found that patients treated with TNFI had a significant decrease in GI, BOP, PD, and serum MMP-3, IL-6, and TNF-α level after 3 months (Kobayashi, Yokoyama et al., 2014) and 6 months (Kobayashi et al., 2015). There were significant improvements in CAL, PD, and BOP in RA patients who were treated with TNFI for 6 months (Ancuta et al., 2017). In contrast, others report increased BOP after 9 months of treatment with TNFI; however, despite increased gingival inflammation (BOP) there were no changes in PD. As CAL was significantly decreased after treatment with infliximab the presence of recessions seems likely (Pers et al., 2008).

Two studies found that RA patients treated with TNFI (receiving no periodontal treatment) demonstrated no significant change in any of the periodontal clinical parameters assessed, namely, PD, CAL, BOP, and GI either 6 weeks (Ortiz et al., 2009) or 6 months of treatment (Fabri et al., 2015). Eventually, Savioli et al. (2012) found that PI was significantly lower for patients with RA and periodontitis treated with TNFI.

When TNFI was compared to other RA treatment schemes, one cross-sectional study found a decrease in inflammation parameters (GI and BOP) and PD in RA patients with TNFI medication compared to RA patients treated with NSAID, glucocorticoids, and csDMARD (Mayer et al., 2009).

One study found lower CAL, less inflammation (lower BOP and GI values), and a lower level of TNF-α in GCF. No difference was found for PD (Mayer et al., 2013). This is in line with another study (Pischon et al., 2008) that showed that RA medication (TNFI, DMARD, corticosteroids, and NSAIDs) had no impact on the number of CAL ≥4 mm and CAL ≤4 mm. One cross-sectional study found no differences in PD, CAL, GI, BOP, or PI between TNFI and csDMARD (Romero-Sanchez et al., 2017). Another cross-sectional study found no impact of TNFI on PISA level (Yamashita et al., 2020).

In addition to periodontal clinical parameters, studies have investigated the microbiological and inflammatory changes in the periodontium following treatment with bDMARDS. An increase of *T. denticola* was reported for patients treated with TNFI alone or in association with other csDMARD and increased *Tannerella forsythia* was found in patients who received TNFI alone (Romero-Sanchez et al., 2017). Treatment with tocilizumab (TCZ) resulted in a significantly greater decrease in gingival inflammation than the TNFI group (Kobayashi et al., 2015).

One cross-sectional study that found TNFI treatment alone or in association with MTX had no impact on any periodontal parameters compared to csDMARD (Mirrielees et al., 2010). However, in this same

study, TNFI treatment decreased the mean level of salivary IL-1β but not of MMP-8 and TNF-α (Mirrielees et al., 2010). Others note that decreased TNF-α levels in GCF accompanied a decreased BOP and GI after 6 weeks of TNFI treatment (Kadkhoda et al., 2016). Similarly, one cross-sectional study found that TNF-α in GCF was significantly lower in patients on infliximab (Mayer et al., 2009), and Üstün et al. (2013) found a significant decrease in GCF IL- 1β, GCF IL-8, salivary IL-8, and salivary MCP-1 levels in RA patients suffering from periodontitis after 30 days of anti-TNF therapy, although they found an increase of gingival inflammation. Systemic changes following treatment with bDMARDS have been studied. Kobayashi et al. (2015) showed that patients on TNFI displayed a significant decrease in serum levels of MMP-3 at 3 and 6 months. Likewise, serum levels of MMP-3, IL-6, and TNF-α were significantly decreased after 3 months of adalimumab therapy in another longitudinal study (Kobayashi, Yokoyama et al., 2014).

B-cell depletion treatment (rituximab and belimumab)

In one longitudinal study, patients treated with RTX showed a significant improvement in PD and CAL but no significant change of PI or GI after 6 months of treatment (Coat et al., 2015). In the same article, authors performed a cross-sectional study that compared one group under MTX that was never under bDMARD to a group that already received at least two courses of two RTX infusions. Patients treated with B-cell depletion treatment (RTX) had better periodontal clinical parameter with lower levels of PD, CAL, PI, and MGI than patients treated with MTX (Coat et al., 2015).

However, one other cross-sectional study found no statistical differences in PD, CAL, PI, and BOP between patients receiving RTX compared with those receiving cDMARD. Nonetheless, GCF IL-1β level was lower in RTX group and GCF MMP-8 level was lower in the other group treated with other cDMARDs (Hatipoğlu et al., 2022).

When B-cell depletion treatment was used in combination with csDMARD, a decrease BOP in patients on RTX + MTX compared to the patients under MTX + TNFI was found (Ziebolz et al., 2018). Wu et al. (2021) found no differences between patients on MTX + RTX and patients under other DMARD.

Impact of other bDMARD (interleukin-6 receptor inhibitor: tocilizumab)

A cohort of patients treated with TCZ demonstrated a significant decrease in GI, BOP, PD, CAL, and serum levels of MMP-3 and TNF-α after 6 months of treatment (Kobayashi et al., 2015). In this study, the impact of TCZ on GI and CAL improvement was significantly greater than TNFI (Kobayashi et al., 2015) although both the TCZ and TNFI groups showed a significant decrease in GI, BOP, and PD at 3 and 6 months. A different cohort reported by the same authors showed TCZ treatment reduced GI and BOP after 8 weeks compared to patients receiving corticosteroid, DMARD, or NSAID (Kobayashi, Okada et al., 2014). The TCZ group showed a significant improvement in PD, CAL, BOP, and GI, whereas the other groups failed to show a significant difference in any periodontal parameter between baseline and follow-up (Kobayashi, Okada et al., 2014). In a longitudinal study, patients treated with TCZ showed a significant decrease in GI, BOP, PD, and CAL after 6 months of treatment (Ancuța et al., 2021).

Regarding *Periodontopathogens*, *Capnocytophaga* species were associated with IL-6 antagonists in one study (Ziebolz et al., 2018) and other report that RTX in association with MTX is associated with reduced number of patients with *T. forsythia* (Wu et al., 2021; Ziebolz et al., 2018).

3.4.4 | Impact of JAK inhibitors (baricitinib and tofacitinib) on periodontal parameters

Only one longitudinal study has investigated the effects of JAK inhibitors on periodontal status in patients with RA (Ancuța et al., 2020). Twenty-one patients with moderate to severe active RA with inadequate response or intolerance to csDMARD or bDMARD were treated with baricitinib. After 24 weeks of treatment, these patients showed a significant improvement in several periodontal clinical parameters, namely, GI, BOP, PD, and number of sites with PD ≥4 mm, there were no significant differences in CAL and PI turned out not to be statistically different (Ancuța et al., 2020).

3.4.5 | Impact of RA combined treatment strategies on periodontal parameters

One cross-sectional study showed that subjects on a combination of MTX and other DMARDs had more severe forms of periodontitis, that is, deeper PD, greater CAL, and higher PI compared to those on monotherapy with MTX (Nik-Azis et al., 2021). In another study, authors found no differences with PD and CAL but worse BOP when patients are under combined MTX and TNFI compared to LM treatment or to MTX + RTX treatment (Ziebolz et al., 2018). One additional cross-sectional study found that all subjects on infliximab in combination with MTX had more inflammation than patients on MTX only (Pers et al., 2008). In another study, the combination of MTX and TNFI showed an increase in gingival inflammation expressed by Papilla Bleeding Index compared to treatment with LM or the combination of MTX with RTX (Wu et al., 2021). These results are consistent with a study of Üstün et al. (2013) who reported a rise in gingival inflammation as expressed by GI and BOP 30 days after treatment change with an association of bDMARD (new treatment) and csDMARD (concomitant medication for 100% of patients). Nevertheless, in this study, GCF IL-1β, GCF IL-8, salivary IL-8, and salivary MCP-1 level decreased significantly after 30 days of treatment.

However, one cohort study found that antirheumatic treatment based on monotherapy with MTX, or anti-TNF in addition to MTX, has a negligible influence on the periodontal condition of RA patients after more than 2 months of treatment (de Smit et al., 2021). One cross-sectional study found that TNFI + MTX was associated with lower extension of interproximal sites with CAL ≥4 mm (Romero-Sanchez et al., 2017).

With regard to periodontopathogens, *T. forsythia* and *Fusobacterium nucleatum* were reported in fewer patients taking MTX + RTX (Wu et al., 2021; Ziebolz et al., 2018). One cross-sectional study reported that the presence of *P. gingivalis* and *Eubacterium nodatum* was significantly associated with the use of more than one DMARD (Romero-Sanchez et al., 2017).

4 | DISCUSSION

This systematic review summarizes the effect of drugs used to treat RA on periodontal parameters.

The DMARDS present an interesting juxtaposition—these drugs are immune-modulatory and likely to render patients more susceptible to infection. However, given their impact on inflammation, some have been experimentally considered possible adjunctive drugs for the treatment of periodontal disease. Therefore, this review sought to delineate how RA treatments impact on the periodontal tissues.

Based on the studies reviewed, NSAIDs and glucocorticoids showed a negligible impact on the periodontium in all studies included in this systematic review of the literature, except for a possible association between corticosteroids and lower GI or tooth loss.

Five studies focusing on csDMARD conclude unanimously that this therapeutic class has a negligible impact on the periodontal clinical parameters (e.g., CAL, PD, BOP, GI, and PI) after 8 weeks to 15.9 months (Äyräväinen et al., 2017, 2018a, 2018b; de Smit et al., 2021; Kobayashi, Okada et al., 2014). The only available longitudinal study on the tsDMARD baricitinib showed a positive impact of this tsDMARD on PD, GI, and BOP after 24 weeks (Ancuța et al., 2020).

Among bDMARDs, TCZ showed positive effects on clinical parameters (CAL, PD, GI, and BOP) and a decrease in serum biomarker levels (MMP-3, IL-6, and TNF-α) (Ancuța et al., 2021; Kobayashi et al., 2015; Kobayashi, Okada et al., 2014). One study on RTX showed positive effects on clinical parameters but no impact on inflammation (Coat et al., 2015). Studies on TNFIs had mixed results. Four longitudinal studies found a positive effect of TNFI on PD, CAL and/or BOP, and GI after 6 weeks to 6 months of treatment (Ancuta et al., 2017; Kadkhoda et al., 2016; Kobayashi et al., 2015; Kobayashi, Yokoyama et al., 2014), whereas two longitudinal studies suggested either negligible or beneficial effects of TNFI treatment on CAL while worsening the gingival inflammation (GI and BOP); thus, the worsening of gingival inflammation seemed disconnected to clinical attachment changes (Pers et al., 2008; Üstün et al., 2013). A further six studies found no effect of TNFI on the periodontium of patients suffering from periodontal disease (Äyräväinen et al., 2017, 2018a, 2018b; de Smit et al., 2021; Fabri et al., 2015; Savioli et al., 2012). The variable findings may reflect study design (baseline prophylaxis, e.g.), extent and severity of periodontitis and/or RA at baseline, potential interactions with concomitant medications, and duration of follow up.

Cross-sectional studies comparing different RA treatments found varying results. In general, bDMARDs were associated with lower BOP compared with other DMARDs (Rovas et al., 2021). However, 10 cross-sectional studies found no significant association between the type of RA treatment and periodontal clinical measurements (Gamel et al., 2017; Hashimoto et al., 2021a, 2021b; Hatipoğlu et al., 2022; Kordtabar et al., 2019; Mirrielees et al., 2010; Ortiz et al., 2009; Pischon et al., 2008; Renvert et al., 2020; Romero-Sanchez et al., 2017; Yamashita et al., 2020). Two cross-sectional studies that measured periodontal biomarkers in GCF or saliva found that IL-1β GCF level was decreased by B-cell depletion treatment, MMP-8 GCF level was lowered by DMARDs (Hatipoğlu et al., 2022) and TNFI decreased IL-1β salivary level (Mirrielees et al., 2010). Nevertheless, although there were differences in biomarkers, these studies concluded there was negligible impact of the type of bDMARD on clinical measures of the periodontium (Romero-Sanchez et al., 2017). There are notable challenges in aligning groups of sufficient size to match for medications and comorbidities—this might partially explain the discrepancies in the results.

Although most studies presented their results as the effect of one RA treatment on the periodontium, most patients took several different RA drugs at the same time. Approximately 30%–40% of patients discontinue their RA treatment due to loss of response, intolerance, or primary treatment failure (Salliot et al., 2011; Wells et al., 2017). To overcome these issues, the 2022 update of the European League Against Rheumatism (EULAR) recommendations for the management of RA suggests that rheumatologists first prescribe MTX + glucocorticoids for 3–6 months. If this therapy fails, any bDMARD should be added to the csDMARD, with the selection of bDMARD left to clinician preference. tsDMARD can eventually be considered instead of bDMARD after careful consideration of the risks of malignancies, cardiovascular, or thromboembolic events. In these cases it is recommended to switch to another bDMARD or to another tsDMARD in order to manage bDMARD treatment failure (Smolen et al., 2023).

Interestingly, combining different RA drugs may have an increased impact on the periodontium. Therefore, TNFI + MTX was associated with an increase of gingival inflammation in 4 studies (Pers et al., 2008; Üstün et al., 2013; Wu et al., 2021; Ziebolz et al., 2018), one study showed that patients under MTX + other DMARD had worse periodontal conditions with higher stage of periodontitis and deeper CAL and PD than patients treated with monotherapy MTX (Nik-Azis et al., 2021; Romero-Sanchez et al., 2017). Baricitinib combined with csDMARD did not appear to exacerbate periodontal inflammation. Feasibly, the RA patients requiring combination therapy have poorly controlled RA and this may of itself be associated with greater propensity to periodontal inflammation.

It could be speculated that if RA symptoms improve patients may be able to perform better oral hygiene—and this, rather than the therapeutic may be responsible for any chances in the periodontal condition. Moreover, there may be effects mediated simply by patients entering studies to investigate their dental health. Looking at dental plaque accumulation, 32 of the 35 studies showed no impact of any RA treatment on PI. Only one of the longitudinal studies found an improvement of PI after 6 months of TNFI (Savioli et al., 2012). In one cross-sectional study, patients on infliximab had lower PI than patients on other RA drugs (Mayer et al., 2013) However, this clinical parameter

was similar to the group of healthy patients with no RA. In one cross-sectional study, authors found a difference in PI between patients under monotherapy MTX and patients on MTX + other DMARD after looking at subgroups. Nevertheless, they found no impact of RA treatment on PI with the groups originally defined (Nik-Azis et al., 2021). Thus, RA treatment seems to have no impact on dental plaque accumulation.

The data suggest that pharmacological treatments for RA may affect the clinical parameters of the periodontium. This is presumed to be a result of the action of these treatments on the inflammatory response; however, the RA treatment may have primary effects on the periodontal microbiota—or secondary effects on the microbiota as the microbiota respond to the different host environment. Three studies included in this systematic review showed that the type of DMARD could affect subgingival microbiota. *T. forsythia* was reported in higher number in patients on monotherapy TNFI and in lower level in patients on MTX + RTX; *P. gingivalis* was reported in higher number of patients on LM, and on MTX + TNFI; *T. denticola* was reported in higher number of patients on NSAID + glucocorticoids, or on MTX, or on LM and the presence of *P. gingivalis* and *E. nodatum* was significantly associated with the use of more than one DMARD (Romero-Sanchez et al., 2017; Wu et al., 2021; Ziebolz et al., 2018).

The data reviewed present both challenges and identifies considerations for futures work. Observational and longitudinal studies are numerous but come up against specific methodological pitfalls. Outcomes are often proxies or surrogates and studies were excluded due to improper outcome measurements or missing data. Periodontal clinical indicators are often heterogeneous, and the source of and type of data shows a considerable variation, some coming from national registers, other from digital cohorts. Not all studies reported detailed concomitant RA treatments, resulting in a limited outcome for the effect of single RA drugs on periodontal status.

Most of the included cross-sectional studies were not primarily designed to evaluate the action of RA treatment on the periodontium. Evaluation of these data could be considered secondary retrospective analysis.

Most of the longitudinal studies focused on TNFI. Further prospective studies are needed to evaluate the possible effect of other DMARD on periodontal status. It is possible that some participants in the included studies were on medication combinations due to the severity of their presenting symptoms and/or the duration of their illness, which resulted in increased disease activity. The comparability of disease activity between subgroups should be considered in the analysis of associations between medication and periodontal condition.

There was a considerable heterogeneity in the activity/severity of RA and RA classification and the severity of periodontal disease and periodontitis classification. Moreover, the presence or absence of anti-citrullinated protein antibodies (ACPA) was rarely assessed. However, the ACPA-positive subset of RA has a more aggressive phenotype, whereas the ACPA-negative subset patients show a less effective treatment response to MTX or RTX (Seegobin et al., 2014).

The review was carried out with systematic review methodology. However, meta-analysis of the data was not possible due to the high heterogeneity of the included studies, which were mostly longitudinal and cross-sectional studies, without any RCTs. The study designs and data presentation showed large heterogeneity and merging of (quantitative) data was not feasible.

We aimed to assess the impact of antirheumatic agents on periodontal conditions of patients suffering from both RA and periodontitis. Although several studies were identified and reviewed, it remains challenging to draw definitive conclusions on the action of RA therapies on periodontal clinical parameters and biomarkers. Many RA therapies are still being tested, and older therapies are often incorporated into treatment protocols (csDMARDs were introduced in the 1970s, bDMARDs appeared in the early 1990s, and tsDMARDs received their first FDA approval in 2012). Nevertheless, in this study, we found that bDMARD and tsDMARD could potentially be beneficial for periodontal health in RA patients with periodontitis. The limited data available suggest that the combination of MTX + TNFI could result in an increased gingival inflammation. Small studies suggest that different type of DMARD was associated with the presence of specific periodontopathogens.

The interdisciplinary approach of the present systematic review of the literature addresses the call for individualized or personalized medicine.

5 | CONCLUSIONS

To date, there are no conclusive data from human studies on the effects of DMARDs on periodontitis due to the small number of patients studied and the absence of RCTs. However, the findings of this systematic review indicate that different pharmacological treatments for RA can affect periodontal clinical parameters. Conventional periodontal therapies have proven safe and reasonably effective in resolving inflammation, halting periodontal tissue destruction, and reducing periodontitis severity regardless RA treatment (Del Rei Daltro Rosa et al., 2021; Nguyen et al., 2021). However, the most used adjunct for periodontal treatment remains systemic antimicrobials. There is an opportunity to learn more from patients taking modulators of inflammation how these drugs might be harnessed as an alternative adjunct to systemic antibiotics. Moreover, it is important to understand the interactions between RA therapies and periodontal health as a personalized medicine approach to optimizing one may benefit the other. Future research should focus on the effects of other DMARDs and the mechanisms underlying the associations between medication and periodontal condition.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

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REFERENCES

Aletaha, D., & Smolen, J. S. (2018). Diagnosis and management of rheumatoid arthritis: A review. *JAMA*, *320*(13), 1360–1372. https://doi.org/10.1001/jama.2018.13103

Ancuta, C., Ancuta, E., Chirieac, R., Antohe, M., & Iordache, C. (2017). Anti-tumor necrosis factor alpha therapy and periodontal inflammation in rheumatoid arthritis. A clinical and biochemical approach. *Revista de Chimie*, *68*(2), 369–372.

Ancuța, C., Chirieac, R., Ancuța, E., Țănculescu, O., Solomon, S. M., Fătu, A. M., Doloca, A., & Iordache, C. (2021). Exploring the role of interleukin-6 receptor inhibitor tocilizumab in patients with active rheumatoid arthritis and periodontal disease. *Journal of Clinical Medicine*, *10*(4), 878. https://doi.org/10.3390/jcm10040878

Ancuța, C., Pomîrleanu, C., Mihailov, C., Chirieac, R., Ancuța, E., Iordache, C., Bran, C., & Țănculescu, O. (2020). Efficacy of baricitinib on periodontal inflammation in patients with rheumatoid arthritis. *Joint Bone Spine*, *87*(3), 235–239. https://doi.org/10.1016/j.jbspin.2019.12.003

Äyräväinen, L., Heikkinen, A. M., Kuuliala, A., Ahola, K., Koivuniemi, R., Laasonen, L., Moilanen, E., Hämäläinen, M., Tervahartiala, T., Meurman, J. H., Leirisalo-Repo, M., & Sorsa, T. (2018a). Inflammatory biomarkers in saliva and serum of patients with rheumatoid arthritis with respect to periodontal status. *Annals of Medicine*, *50*(4), 333–344. https://doi.org/10.1080/07853890.2018.1468922

Äyräväinen, L., Heikkinen, A. M., Kuuliala, A., Ahola, K., Koivuniemi, R., Moilanen, E., Hämäläinen, M., Tervahartiala, T., Meurman, J. H., Leirisalo-Repo, M., & Sorsa, T. (2018b). Anti-rheumatic medication and salivary MMP-8, a biomarker for periodontal disease. *Oral Diseases*, *24*(8), 1562–1571. https://doi.org/10.1111/odi.12930

Äyräväinen, L., Leirisalo-Repo, M., Kuuliala, A., Koivuniemi, R., Meurman, J. H., & Heikkinen, A. M. (2017). Periodontitis in early and chronic rheumatoid arthritis: A prospective follow-up study in Finnish population. *BMJ Open*, *7*, e011916. https://doi.org/10.1136/bmjopen-2016-011916

Coat, J., Demoersman, J., Beuzit, S., Cornec, D., Devauchelle-Pensec, V., Saraux, A., & Pers, J.-O. (2015). Anti-B lymphocyte immunotherapy is associated with improvement of periodontal status in subjects with rheumatoid arthritis. *Journal of Clinical Periodontology*, *42*(9), 817–823. https://doi.org/10.1111/jcpe.12433

Del Rei Daltro Rosa, C. D., de Luna Gomes, J. M., Dantas de Moraes, S. L., Araujo Lemos, C. A., Minatel, L., Justino de Oliveira Limirio, J. P., & Pellizzer, E. P. (2021). Does non-surgical periodontal treatment influence on rheumatoid arthritis? A systematic review and meta-analysis. *The Saudi Dental Journal*, *33*(8), 795–804. https://doi.org/10.1016/j.sdentj.2021.09.007

de Pablo, P., Chapple, I. L. C., Buckley, C. D., & Dietrich, T. (2009). Periodontitis in systemic rheumatic diseases. *Nature Reviews. Rheumatology*, *5*(4), 218–224. https://doi.org/10.1038/nrrheum.2009.28

de Pablo, P., Dietrich, T., & McAlindon, T. E. (2008). Association of periodontal disease and tooth loss with rheumatoid arthritis in the US population. *The Journal of Rheumatology*, *35*(1), 70–76.

de Smit, M. J., Westra, J., Posthumus, M. D., Springer, G., van Winkelhoff, A. J., Vissink, A., Brouwer, E., & Bijl, M. (2021). Effect of anti-rheumatic treatment on the periodontal condition of rheumatoid arthritis patients. *International Journal of Environmental Research and Public Health*, *18*(5), 2529. https://doi.org/10.3390/ijerph18052529

Eke, P. I., Page, R. C., Wei, L., Thornton-Evans, G., & Genco, R. J. (2012). Update of the case definitions for population-based surveillance of periodontitis. *Journal of Periodontology*, *83*(12), 1449–1454. https://doi.org/10.1902/jop.2012.110664

Fabri, G. M. C., Pereira, R. M. R., Savioli, C., Saad, C. G. S., de Moraes, J. C. B., Siqueira, J. T. T., & Bonfa, E. (2015). Periodontitis response to anti-TNF therapy in ankylosing spondylitis. *Journal of Clinical Rheumatology: Practical Reports on Rheumatic & Musculoskeletal Diseases*, *21*(7), 341–345. https://doi.org/10.1097/RHU.0000000000000300

Gamel, E. B., Hashim, N. T., Satti, A., & Gismalla, B. G. (2017). Salivary TNFα levels in groups of subjects with rheumatoid arthritis and chronic periodontitis. *BMC Research Notes*, *10*(10), 34. https://doi.org/10.1186/s13104-016-2341-7

Genco, R. J., & Sanz, M. (2020). Clinical and public health implications of periodontal and systemic diseases: An overview. *Periodontology*, *83*(1), 7–13. https://doi.org/10.1111/prd.12344

Hajishengallis, G. (2022). Interconnection of periodontal disease and comorbidities: Evidence, mechanisms, and implications. *Periodontology 2000*, *89*(1), 9–18. https://doi.org/10.1111/prd.12430

Hashimoto, H., Hashimoto, S., & Shimazaki, Y. (2021a). Association between the extent of periodontal inflammation and the severity of rheumatoid arthritis in Japanese patients with rheumatoid arthritis. *International Dental Journal*, *71*(5), 429–437. https://doi.org/10.1016/j.identj.2020.12.015

Hashimoto, H., Hashimoto, S., & Shimazaki, Y. (2021b). Relationship between tooth loss and the medications used for the treatment of rheumatoid arthritis in Japanese patients with rheumatoid arthritis: A cross-sectional study. *Journal of Clinical Medicine*, *10*(4), 876. https://doi.org/10.3390/jcm10040876

Hatipoğlu, M., Daltaban, Ö., Uğur, S., Üstün, K., Kaçar, C., Tuncer, T., & Kantarci, A. (2022). B cell depletion in patients with rheumatoid arthritis is associated with reduced IL-1β in GCF. *Clinical Oral Investigations*, *26*(6), 4307–4313. https://doi.org/10.1007/s00784-022-04378-0

Jung, G.-U., Han, J.-Y., Hwang, K.-G., Park, C.-J., Stathopoulou, P. G., & Fiorellini, J. P. (2018). Effects of conventional synthetic disease-modifying antirheumatic drugs on response to periodontal treatment in patients with rheumatoid arthritis. *BioMed Research International*, *2018*, 1465402. https://doi.org/10.1155/2018/1465402

Kadkhoda, Z., Amirzargar, A., Esmaili, Z., Vojdanian, M., & Akbari, S. (2016). Effect of TNF-α blockade in gingival crevicular fluid on periodontal condition of patients with rheumatoid arthritis. *Iranian Journal of Immunology: IJI*, *13*(3), 197–203.

Kassebaum, N. J., Bernabé, E., Dahiya, M., Bhandari, B., Murray, C. J. L., & Marcenes, W. (2014). Global burden of severe periodontitis in 1990–2010: A systematic review and meta-regression. *Journal of Dental Research*, *93*(11), 1045–1053. https://doi.org/10.1177/0022034514552491

Kim, J.-W., & Suh, C.-H. (2020). Systemic manifestations and complications in patients with rheumatoid arthritis. *Journal of Clinical Medicine*, *9*(6), 2008. https://doi.org/10.3390/jcm9062008

Kobayashi, T., Ito, S., Kobayashi, D., Kojima, A., Shimada, A., Narita, I., Murasawa, A., Nakazono, K., & Yoshie, H. (2015). Interleukin-6 receptor inhibitor tocilizumab ameliorates periodontal inflammation in patients with rheumatoid arthritis and periodontitis as well as tumor necrosis factor inhibitors. *Clinical and Experimental Dental Research*, *1*(2), 63–73. https://doi.org/10.1002/cre2.11

Kobayashi, T., Okada, M., Ito, S., Kobayashi, D., Ishida, K., Kojima, A., Narita, I., Murasawa, A., & Yoshie, H. (2014). Assessment of interleukin-6 receptor inhibition therapy on periodontal condition in patients with rheumatoid arthritis and chronic periodontitis. *Journal of Periodontology*, *85*(1), 57–67. https://doi.org/10.1902/jop.2013.120696

Kobayashi, T., Yokoyama, T., Ito, S., Kobayashi, D., Yamagata, A., Okada, M., Oofusa, K., Narita, I., Murasawa, A., Nakazono, K., & Yoshie, H. (2014). Periodontal and serum protein profiles in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitor adalimumab. *Journal of Periodontology*, *85*(11), 1480–1488. https://doi.org/10.1902/jop.2014.140194

Kobayashi, T., & Yoshie, H. (2015). Host responses in the link between periodontitis and rheumatoid arthritis. *Current Oral Health Reports*, *2*(1), 1–8. https://doi.org/10.1007/s40496-014-0039-2

Kordtabar, S., Aghaie, M., Fakhari, E., & Vakili, M. A. (2019). Periodontal condition in patients with rheumatoid arthritis: Effect of anti-rheumatic drugs. *Journal of Dentistry (Shiraz, Iran)*, *20*(3), 190–194. https://doi.org/10.30476/DENTJODS.2019.44914

Koziel, J., & Potempa, J. (2022). Pros and cons of causative association between periodontitis and rheumatoid arthritis. *Periodontology 2000*, *89*(1), 83–98. https://doi.org/10.1111/prd.12432

Mayer, Y., Balbir-Gurman, A., & Machtei, E. E. (2009). Anti-tumor necrosis factor-alpha therapy and periodontal parameters in patients with rheumatoid arthritis. *Journal of Periodontology*, *80*(9), 1414–1420. https://doi.org/10.1902/jop.2009.090015

Mayer, Y., Elimelech, R., Balbir-Gurman, A., Braun-Moscovici, Y., & Machtei, E. E. (2013). Periodontal condition of patients with autoimmune diseases and the effect of anti-tumor necrosis factor-α therapy. *Journal of Periodontology*, *84*(2), 136–142. https://doi.org/10.1902/jop.2012.120009

Mirrielees, J., Crofford, L. J., Lin, Y., Kryscio, R. J., Dawson, D. R., Ebersole, J. L., & Miller, C. S. (2010). Rheumatoid arthritis and salivary biomarkers of periodontal disease. *Journal of Clinical Periodontology*, *37*(12), 1068–1074. https://doi.org/10.1111/j.1600-051X.2010.01625.x

Nguyen, V. B., Nguyen, T. T., Huynh, N. C.-N., Nguyen, K. D., Le, T. A., & Hoang, H. T. (2021). Effects of non-surgical periodontal treatment in rheumatoid arthritis patients: A randomized clinical trial. *Dental and Medical Problems*, *58*(1), 97–105. https://doi.org/10.17219/dmp/131266

Nik-Azis, N.-M., Mohd, N., Mohd Fadzilah, F., Mohamed Haflah, N. H., Mohamed Said, M. S., & Baharin, B. (2021). Rheumatoid arthritis serotype and synthetic disease-modifying anti-rheumatic drugs in patients with periodontitis: A case-control study. *PLoS ONE*, *16*(6), e0252859. https://doi.org/10.1371/journal.pone.0252859

Ortiz, P., Bissada, N. F., Palomo, L., Han, Y. W., Al-Zahrani, M. S., Panneerselvam, A., & Askari, A. (2009). Periodontal therapy reduces the severity of active rheumatoid arthritis in patients treated with or without tumor necrosis factor inhibitors. *Journal of Periodontology*, *80*(4), 535–540. https://doi.org/10.1902/jop.2009.080447

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ (Clinical Research Ed.)*, *372*, n71. https://doi.org/10.1136/bmj.n71

Pearson, A., Jordan, Z., Lockwood, C., & Aromataris, E. (2015). Notions of quality and standards for qualitative research reporting. *International Journal of Nursing Practice*, *21*(5), 670–676. https://doi.org/10.1111/ijn.12331

Pers, J.-O., Saraux, A., Pierre, R., & Youinou, P. (2008). Anti-TNF-alpha immunotherapy is associated with increased gingival inflammation without clinical attachment loss in subjects with rheumatoid arthritis. *Journal of Periodontology*, *79*(9), 1645–1651. https://doi.org/10.1902/jop.2008.070616

Pihlstrom, B. L., Michalowicz, B. S., & Johnson, N. W. (2005). Periodontal diseases. *Lancet (London, England)*, *366*(9499), 1809–1820. https://doi.org/10.1016/S0140-6736(05)67728-8

Pischon, N., Pischon, T., Kröger, J., Gülmez, E., Kleber, B.-M., Bernimoulin, J.-P., Landau, H., Brinkmann, P.-G., Schlattmann, P., Zernicke, J., Buttgereit, F., & Detert, J. (2008). Association among rheumatoid arthritis, oral hygiene, and periodontitis. *Journal of Periodontology*, *79*(6), 979–986. https://doi.org/10.1902/jop.2008.070501

Qiao, Y., Wang, Z., Li, Y., Han, Y., Zhou, Y., & Cao, X. (2020). Rheumatoid arthritis risk in periodontitis patients: A systematic review and meta-analysis. *Joint Bone Spine*, *87*(6), 556–564. https://doi.org/10.1016/j.jbspin.2020.04.024

Renvert, S., Berglund, J. S., Persson, G. R., & Söderlin, M. K. (2020). The association between rheumatoid arthritis and periodontal disease in a population-based cross-sectional case-control study. *BMC Rheumatology*, *4*, 31. https://doi.org/10.1186/s41927-020-00129-4

Rodríguez-Lozano, B., González-Febles, J., Garnier-Rodríguez, J. L., Dadlani, S., Bustabad-Reyes, S., Sanz, M., Sánchez-Alonso, F., Sánchez-Piedra, C., González-Dávila, E., & Díaz-González, F. (2019). Association between severity of periodontitis and clinical activity in rheumatoid arthritis patients: A case–control study. *Arthritis Research & Therapy*, *21*(1), 27. https://doi.org/10.1186/s13075-019-1808-z

Romero-Sanchez, C., Rodríguez, C., Santos-Moreno, P., Mesa, A. M., Lafaurie, G. I., Giraldo-Q, S., De-Avila, J., Castillo, D. M., Duran, M., Chalem, P. C., Bello Gualtero, J. M., & Valle-Oñate, R. (2017). Is the treatment with biological or non-biological DMARDS a modifier of periodontal condition in patients with rheumatoid arthritis? *Current Rheumatology Reviews*, *13*(2), 139–151. https://doi.org/10.2174/1573397113666170407161520

Rovas, A., Puriene, A., Punceviciene, E., Butrimiene, I., Stuopelyte, K., & Jarmalaite, S. (2021). Associations of periodontal status in periodontitis and rheumatoid arthritis patients. *Journal of Periodontal & Implant Science*, *51*(2), 124–134. https://doi.org/10.5051/jpis.2006060303

Salliot, C., Finckh, A., Katchamart, W., Lu, Y., Sun, Y., Bombardier, C., & Keystone, E. (2011). Indirect comparisons of the efficacy of biological antirheumatic agents in rheumatoid arthritis in patients with an inadequate response to conventional disease-modifying antirheumatic drugs or to an anti-tumour necrosis factor agent: A meta-analysis. *Annals of the Rheumatic Diseases*, *70*(2), 266–271. https://doi.org/10.1136/ard.2010.132134

Savioli, C., Ribeiro, A. C. M., Fabri, G. M. C., Calich, A. L., Carvalho, J., Silva, C. A., Viana, V. S. T., Bonfá, E., & Siqueira, J. T. T. (2012). Persistent periodontal disease hampers anti-tumor necrosis factor treatment response in rheumatoid arthritis. *Journal of Clinical Rheumatology: Practical Reports on Rheumatic & Musculoskeletal Diseases*, *18*(4), 180–184. https://doi.org/10.1097/RHU.0b013e31825828be

Schmalz, G., Bartl, M., Schmickler, J., Patschan, S., Patschan, D., & Ziebolz, D. (2021). Tooth loss is associated with disease-related parameters in patients with rheumatoid arthritis and ankylosing spondylitis—A cross-sectional study. *Journal of Clinical Medicine*, *10*(14), 3052. https://doi.org/10.3390/jcm10143052

Seegobin, S. D., Ma, M. H. Y., Dahanayake, C., Cope, A. P., Scott, D. L., Lewis, C. M., & Scott, I. C. (2014). ACPA-positive and ACPA-negative rheumatoid arthritis differ in their requirements for combination DMARDs and corticosteroids: Secondary analysis of a randomized controlled trial. *Arthritis Research & Therapy*, *16*(1), R13. https://doi.org/10.1186/ar4439

Silman, A. J., & Pearson, J. E. (2002). Epidemiology and genetics of rheumatoid arthritis. *Arthritis Research*, *4*(Suppl 3), S265–S272. https://doi.org/10.1186/ar578

Smolen, J. S., Landewé, R. B. M., Bergstra, S. A., Kerschbaumer, A., Sepriano, A., Aletaha, D., Caporali, R., Edwards, C. J., Hyrich, K. L., Pope, J. E., de Souza, S., Stamm, T. A., Takeuchi, T., Verschueren, P., Winthrop, K. L., Balsa, A., Bathon, J. M., Buch, M. H., Burmester, G. R., … van der Heijde, D. (2023). EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Annals of the Rheumatic Diseases*, *82*(1), 3–18. https://doi.org/10.1136/ard-2022-223356

Üstün, K., Erciyas, K., Kısacık, B., Sezer, U., Pehlivan, Y., Öztuzcu, S., Gündoğar, H., & Onat, A. M. (2013). Host modulation in rheumatoid arthritis patients with TNF blockers significantly decreases biochemical parameters in periodontitis. *Inflammation*, *36*(5), 1171–1177. https://doi.org/10.1007/s10753-013-9652-9

Wells, A. F., Curtis, J. R., Betts, K. A., Douglas, K., Du, E. X., & Ganguli, A. (2017). Systematic literature review and meta-analysis of tumor necrosis factor-alpha experienced rheumatoid arthritis. *Clinical Therapeutics*, *39*(8), 1680–1694.e2. https://doi.org/10.1016/j.clinthera.2017.06.013

Wells, G. A, Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [cited 2023 Oct 19].

Available from: http://www.ohrica/programs/clinical_epidemiology/oxfordasp

Wu, Z., Yang, X., & Li, N. (2021). Effects of different immunosuppressive drugs on the periodontal status and changes in periodontal pathogenic bacterial flora in rheumatoid arthritis patients. *Tropical Journal of Pharmaceutical Research*, *20*(10), 2219–2226. https://doi.org/10.4314/tjpr.v20i10.29

Yamashita, M., Kobayashi, T., Ito, S., Kaneko, C., Murasawa, A., Ishikawa, H., & Tabeta, K. (2020). The periodontal inflamed surface area is associated with the clinical response to biological disease-modifying antirheumatic drugs in rheumatoid arthritis: A retrospective study. *Modern Rheumatology*, *30*(6), 990–996. https://doi.org/10.1080/14397595.2019.1680100

Ziebolz, D., Rupprecht, A., Schmickler, J., Bothmann, L., Krämer, J., Patschan, D., Müller, G. A., Mausberg, R. F., Schmidt, J., Schmalz, G., & Patschan, S. (2018). Association of different immunosuppressive medications with periodontal condition in patients with rheumatoid arthritis: Results from a cross-sectional study. *Journal of Periodontology*, *89*(11), 1310–1317. https://doi.org/10.1002/JPER.17-0616

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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